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Volume One

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Plastic Surgery

Principles

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Fourth Edition

Plastic Surgery



Principles

Volume One

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Reduction mammoplasty with inverted-T techniques

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Maurice Y. Nahabedian, Phillip N. Blondeel, and David H. Song

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Chapter 37: Restoration of upper extremity function in tetraplegia

Restoration of upper extremity function in tetraplegia*Carina Reinholdt and Catherine Curtin*



Preface to the Fourth Edition

When I wrote the preface to the 3rd edition of this book, I remarked how honored and unexpectedly surprised I was to be the Editor of this great series. This time 'round, I'm equally grateful to carry this series forward. When Elsevier called me and suggested it was time to prepare the 4th edition, my initial reaction was that this was way too soon. What could possibly have changed in Plastic Surgery since the 3rd edition was launched in 2012? As it transpires, there have been many developments and I hope we have captured them in this edition.

We have an extraordinary specialty. A recent article by Chadra, Agarwal and Agarwal entitled "Redefining Plastic Surgery" appeared in *Plastic and Reconstructive Surgery—Global Open*. In it they gave the following definition: "Plastic surgery is a specialized branch of surgery, which deals with deformities, defects and abnormalities of the organs of perception, organs of action and the organs guarding the external passages, besides innovation, implantation, replantation and transplantation of tissues, and aims at restoring and improving their form, function and the esthetic appearances." This is an all-encompassing but very apt definition and captures the enormous scope of the specialty.¹

In the 3rd edition, I introduced volume editors for each of the areas of the specialty because the truth is that one person can no longer be an expert in all areas of this diverse specialty, and I'm certainly not. I think this worked well because the volume editors not only had the expertise to present their area of subspecialty in the best light, but they were tuned in to what was new and who was doing it. We have continued this model in this new edition. Four of the seven volume editors from the previous edition have again helped to bring the latest and the best to this edition: Drs Gurtner, Song, Rodriguez, Losee, and Chang have revised and updated their respective volumes with some chapters remaining, some extensively revised, some added, and some deleted. Dr. Peter Rubin has replaced Dr. Rick Warren to compile the Aesthetic volume (Vol. 2). Dr. Warren did a wonderful job in corralling this somewhat disparate, yet vitally important, part of our specialty into the Aesthetic volume in the 3rd edition but felt that the task of doing it again, though a labor of love, was more than he wanted to take on. Similarly, Dr. Jim Grotting who did a masterful job in the last edition on the Breast volume, decided that doing a major revision should be undertaken by someone with a fresh perspective and Dr. Maurice Nahabedian stepped into that breach. I hope you will like the changes you see in both of these volumes.

Dr. Allen Van Beek was the video editor for the last edition and he compiled an impressive array of movies to complement the text. This time around, we wanted to go a step further and though we've considerably expanded the list of

videos accompanying the text (there are over 170), we also added the idea of lectures accompanying selected chapters. What we've done here is to take selected key chapters and include the images from that chapter, photos and artwork, and create a narrated presentation that is available online; there are annotations in the text to alert the reader that this is available. Dr. Daniel Liu, who has taken over from Dr. Van Beek as multimedia editor (rather than video editor) has done an amazing job in making all of this happen. There are over 70 presentations of various key chapters online, making it as easy as possible for you, the reader, to get as much knowledge as you can, in the easiest way possible from this edition. Many of these presentations have been done by the authors of the chapters; the rest have been compiled by Dr. Liu and myself from the content of the individual chapters. I hope you find them useful.

The reader may wonder how this all works. To plan this edition, the Elsevier team, headed by Belinda Kuhn, and I, convened a face-to-face meeting in San Francisco. The volume editors, as well as the London based editorial team, were present. We went through the 3rd edition, volume by volume, chapter by chapter, over an entire weekend. We decided what needed to stay, what needed to be added, what needed to be revised, and what needed to be changed. We also decided who should write the various chapters, keeping many existing authors, replacing others, and adding some new ones; we did this so as to really reflect the changes occurring within the specialty. We also decided on practical changes that needed to be made. As an example, you will notice that we have omitted the complete index for the 6 Volume set from Volumes 2-6 and highlighted only the table of contents for that particular volume. The complete index is of course available in Volume 1 and fully searchable online. This allowed us to save several hundred pages per volume, reducing production costs and diverting those dollars to the production of the enhanced online content.

In my travels around the world since the 3rd edition was published, I've been struck by what an impact this publication has had on the specialty and, more particularly, on training. Everywhere I go, I'm told how the text is an important part of didactic teaching and a font of knowledge. It is gratifying to see that the 3rd edition has been translated into Portuguese, Spanish, and Chinese. This is enormously encouraging. I hope this 4th edition continues to contribute to the specialty, remains a resource for practicing surgeons, and continues to prepare our trainees for their future careers in Plastic Surgery.

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September, 2017

¹ Chandra R, Agarwal R, Agarwal D. Redefining Plastic Surgery. *Plast Reconstr Surg Glob Open*. 2016;4(5):e706.

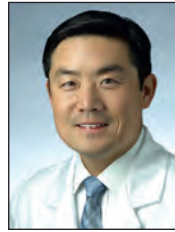
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Peter C. Neligan, MB, FRCS(I), FRCSC, FACS

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Geoffrey C. Gurtner, MD, FACS

*Dedicated to future plastic surgeons. Take up the torch
and lead us forward!*

Plastic surgery and innovation in medicine

Peter C. Neligan

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SYNOPSIS

- There is a major difference between research and innovation, though the two are often interrelated.
- Most advances in surgery come from innovation rather than basic research.
- Surgical innovation is one of the defining features of plastic surgery.
- Surgical innovation is made safe by defining principles.
- A detailed knowledge of anatomy is a major factor on which these principles are based.
- A balance between out-of-the-box thinking and conservative deliberation is the perfect milieu to effect change yet keep perspective.

Introduction

There was a time when a general surgeon took care of everything; from fractures to furuncles, skin grafts to sigmoidoscopies, cysts to cancers. Since that time, everything has become specialized. Even in our specialty, the era of subspecialization has already arrived. Despite this, in some ways plastic surgeons are the last general surgeons. We are not confined to an organ or system. Nor are we linked to a disease, and this separates us from almost every other medical specialty. With some exceptions, plastic surgery operations are not always the same. We regularly perform operations that we've never done in precisely the same way before and will likely never do in exactly the same way again. We almost always have completed some elements of the surgery before, or we may add elements from another sphere of surgery to create a new approach to a problem. The adoption of endoscopic techniques is an example of this.

Sometimes this innovation is born of necessity, the challenge of solving a unique problem for which there is no standard or well-accepted solution. Sometimes it is born of the will to do something better, to solve a problem in such a way that is better than what has been done before. The time

of greatest surgical innovation in most specialties is in times of war and natural disaster when we are presented with problems in such overwhelming numbers that we have to come up with some solution that enables us to deal with such large numbers. While this is acceptable in these unique situations, the concept of innovation at other times is sometimes shocking to non-medical people. To the uninitiated it may seem cavalier, even dangerous. However, these innovations are based on principles that we learn in our training and that we apply in our practice. That is the magic of plastic surgery and what many people have called the art of plastic surgery. It is in many ways similar to the musician who tries a new way of interpreting a song or a painter who uses new materials to paint a picture, though my personal view is that plastic surgery is more a craft than an art. Of course this type of surgical innovation raises ethical issues and it is something with which many institutions are struggling, not merely in the domain of plastic surgery but in the field of surgery in general.¹ In 2008, a position statement of the Society of University Surgeons (SUS) recommended the creation of institutional surgical innovation committees (SICs) to ensure appropriate oversight of surgical innovations. It is surprising that several years later, only 23% of surgery departments had SICs in place and many department chairs were unaware of the position statement.² Many institutions already have processes and protocols in place to oversee and regulate innovation.³ When is innovation in surgery ethical and when is it not? This has already been the source of much discussion in the literature.⁴⁻⁶ How far can we safely push the envelope? That particular discussion is beyond the scope of this chapter. In order to push the frontiers of surgery it is important to strike a balance between necessary oversight of research practices and a supportive environment where research can flourish.

Innovation and research

What is the difference between innovation and research? Wikipedia (<http://en.wikipedia.org/wiki/Research>) defines

research as follows: “Research comprises ‘creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of humans, culture and society, and the use of this stock of knowledge to devise new applications.’” The definition of innovation is much different: (<http://en.wikipedia.org/wiki/Innovation>) “The term ‘innovation’ can be defined as something original and more effective and, as a consequence, new, that ‘breaks into’ the market or society.” It may refer to an incremental emergent change or radical and revolutionary changes in thinking, products, processes, or organizations.” Though we would like to think that innovation comes from research, this is not always the case. It’s not just in medicine that this happens. For example, innovations in the computer industry are often simple changes introduced to facilitate a task, only to sometimes completely change how things are done. For instance, Apple recently redesigned laptop batteries to completely fill the irregular space available and thereby prolong battery life. They have also revolutionized how we listen to music, and how we even purchase it. New changes happen all the time; they are sometimes incremental and sometimes game-changing.

Most of the surgical innovations we see are not the result of research and, historically, most of the major advances in surgery have been the result of innovation rather than basic research. In fact, not infrequently, an innovation, often conceived on the fly, is subsequently subjected to more rigorous study. A surgeon may design a new operation or, for example, a new flap. This may be a variation on an old procedure or sometimes something completely new. As I have already said, it may have been forced on the surgeon because of the circumstances of the case. There may be no other way to solve the problem. When it works, the surgeon decides to design a study to explain why the procedure worked or to describe the blood supply of the flap. Though one could argue that this is not the ideal way to do things, it certainly happens^{7,8} and is merely a reflection of the dynamic nature of surgical innovation. Innovation may be planned or, in the case of this example and as happens probably more frequently, may be made on the fly. Research may be innovative. A researcher may design a novel experiment to probe a theory, an approach to the problem that has not been explored before. This is also innovation and is more commonly how research and innovation are linked. An innovative idea is subjected to the scientific method that research demands. What makes an innovator? It has been said that the characteristics that most major innovators have in common include: 1) the ability to recognize an idea, 2) persistence in developing the strategy and 3) commitment to the project, and final completion of a response to the problem or problems in question.⁹

Innovation and plastic surgery

The history of plastic surgery, at least the history of modern plastic surgery, is one of constant development. We regularly devise new ways of dealing with a particular problem. We develop a technique, perfect it and then either lose it to some other group, or give it away. There are numerous examples of this, from cleft surgery to microsurgery, from hand surgery to craniofacial surgery. While some see this as a major problem, I would argue that it is the lifeblood of plastic surgery. We are constantly developing new solutions to diverse problems.

Some of these problems are generated from within our own practices, some come from our interaction with other specialties. We develop solutions and frequently allow those other specialties to run with the ball while we go on to something else. The facility to adapt is important in all spheres. For example, this ability to adapt, change and incorporate new ideas is what has made English such a dominant language. It is the reason that Apple Inc. has become an industry leader. This is the essence of innovation. There are numerous examples in biology that underline how the power of adaption is the power of survival. For plastic surgery the same holds true and while some fear the demise of the specialty, I would argue that while we continue to adapt and develop, there will always be a place for plastic surgery.

Vascularized composite allotransplantation

In research we work with models; models of disease, models of a procedure. Animal models provide a means by which we can study the process we are interested in addressing in our patients. Occasionally, in order to solve a problem, we move to models that are perhaps less relevant to our everyday clinical practice. For example, most people don’t realize that the first kidney transplant was performed by Dr. Joseph Murray (Fig. 1.1), a plastic surgeon at the Peter Bent Brigham Hospital in Boston,¹⁰ now the Brigham and Women’s Hospital. People are generally intrigued by this snippet of information. What was a plastic surgeon doing transplanting kidneys? How could this be? His practice as a plastic surgeon raised questions in his mind surrounding transplantation. His experience treating burn patients sent back from the war during World War II gave him wide exposure to skin grafting and raised issues of immune rejection that he would later find ways to address. In trying to work out the immunology of skin grafts, he moved to a single organ model, the kidney, in order to answer the question he had originally conceived. This

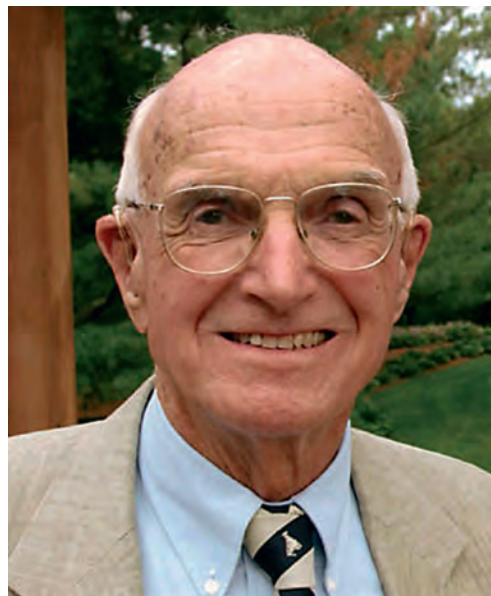


Fig. 1.1 Dr. Joseph Murray.

culminated in the first successful kidney transplant performed from one twin to another by Dr. Murray at the Peter Bent Brigham Hospital in Boston in 1954. Having helped develop the specialty of transplantation, he went on to perform the world's first successful allograft in 1959 and the world's first cadaveric renal transplant in 1962. Dr. Murray ultimately returned to his roots, the practice of plastic surgery, and was awarded the Nobel Prize in Physiology or Medicine in 1990 for his contribution to the science of transplantation.

Now, that wheel has turned full circle and plastic surgery is, once again, in the mainstream of transplant innovation (see Chapter 32). Hand and face transplants have become a reality. The first hand transplant was performed in 1998¹¹ and the first face transplant in 2005.¹² While these procedures are still not in the mainstream of practice, it is interesting that there are 20 institutions designated as VCA (vascularized composite allograft) transplant centers in the US and three of them have established their programs as standard of care rather than submitting them under an institutional review board (IRB) protocol. This has been accepted by UNOS (United Network for Organ Sharing), the private, non-profit organization that manages the US organ transplant system under contract with the federal government. VCA is designed to address those reconstructions that we cannot realistically achieve with conventional reconstructive techniques. Because immunosuppression to prevent rejection is such an onerous undertaking for the patient, VCA is currently restricted to major transplants. However, at some stage we will figure out a better and safer way to prevent rejection and then VCA will include transplantation of functioning eyelids, noses, ears, tongue and other specialized organs, all the areas that we currently can't effectively reconstruct with conventional techniques. While total nasal reconstruction, as an example, has attained a high level of sophistication, the truth is that elegant total nasal reconstructions are achieved by only a small number of expert surgeons utilizing very complex techniques in a series of operations over a period of months or years. The concept of a surgeon being able to transplant a nose in a single stage and achieve an elegant result is very attractive. The same is true for many other body parts, such as ears, tongue, genitalia, etc. In fact, penile transplantations have already become a reality. Obviously many obstacles remain before we will see this range of transplants in practice. VCA is a perfect example of how an innovative technical advance engenders increased research activity. The barrier to successful transplantation is not a technical one, it is an immunologic one and current interest in VCA has spawned a new wave of research activity in the field of immunology. This demands a collaborative and multidisciplinary approach, something that, again, plastic surgeons do well.

Collaboration

Plastic surgeons cannot lay claim to being the only innovators in medicine. Medicine is full of innovators. Yet it is true that the nature of the plastic surgeon's work, more than many other specialties, demands innovation. And that is what most plastic surgeons do every day of the week. Because so much of what we do, particularly in reconstructive surgery, is in collaboration with other specialties, innovation in those areas of practice often lead to innovations in our field. Most of the innovations we see are incremental. A surgeon incrementally changes how



Fig. 1.2 Dr. Paul Tessier. (Courtesy of Barry M Jones.)

(s)he practices or how (s)he does a particular operation. Every now and again the innovation is radical. The development of craniofacial surgery is an example of radical innovation. Paul Tessier (Fig. 1.2) was the first to describe a combined intra- and extracranial approach for the correction of hypertelorism,^{13,14} breaking the previously held taboo of exposing the intracranial environment to the upper aerodigestive tract. Going against the surgical mainstream demands unimaginable courage. It takes pioneers like Dr. Tessier to have the courage of their convictions, or the obstinacy to push the envelope beyond the general comfort level. Apart from spawning the specialty of craniofacial surgery, Dr. Tessier's advances led to advances in related fields. An interesting footnote is that we now rarely see cases of hypertelorbitism, presumably because they are detected in utero and the fetuses aborted.

One of the related fields that Dr. Tessier's work influenced is that of skull base surgery. The craniofacial principles developed by Dr. Tessier literally opened this field. Tumors that were previously considered inoperable and inaccessible became treatable. That progress led to further innovations. So, continuing with the example of skull base surgery, the radical resections and approaches that were developed in the 1970s and 80s^{15,16} created complications such as meningitis, brain abscesses and problems related to delayed wound healing. Smaller defects could be closed with local flaps such as pericranial flaps, or galeafrontalis flaps.¹⁷ However, larger defects remained a problem until free flaps were used to close these defects.^{18,19} Then the incidence of all of the complications, the brain abscesses, meningitis and wound healing problems, were dramatically reduced and the surgery became safer. So microvascular surgery made skull base tumor surgery safer. More recently in this field we have seen innovations in the surgical approaches to the skull base facilitate the development of endoscopic skull base surgery. Large resections are



Fig. 1.3 The Editor and Dr. Joe McCarthy at the launch of *Plastic Surgery*, 3rd edition.

now feasible through an endoscopic approach. This development has had a large impact on these patients because extensive open approaches, with the associated risks of scarring and deformity, are no longer necessary. However, with these large endoscopic resections, we are seeing the re-emergence of problems such as meningitis and abscess because of the difficulty in reconstructing these defects endoscopically.²⁰ This has led to the development of new reconstructive techniques and approaches in order to address these complications.^{21–23} This is an excellent example of how a multidisciplinary approach can advance a field. An innovation in one area can create a problem in another area that forces further innovation.

Similarly, an innovation in another specialty can change the way we practice in ours. An example is the introduction of bone lengthening procedures by Dr. Gavril Ilizarov.²⁴ This was revolutionary in the 1960s. That technology was adapted by Dr. Joseph McCarthy (Fig. 1.3) and applied to the craniofacial skeleton.^{25–27} This innovation has changed the way many craniofacial deformities are treated. Dr. McCarthy, incidentally, edited the first edition of *Plastic Surgery*.

Progress in surgery, regardless of specialty, demands a balance between innovators and conservatives. Innovators push the envelope and work best when they are paired with conservatives who rein them in to a degree. Thus, a balance between out-of-the-box thinking and conservative

deliberation is the perfect milieu to effect change yet keep perspective.

Drivers of innovation

As already mentioned, innovation is also forced in times of upheaval and change. The classic examples are war and natural disasters. More surgical advances are made in wartime than in peacetime. This is because specific problems are seen in unprecedented numbers and demand a solution. In this sort of environment it becomes reasonable to break the rules. One has to, simply, cope. Out of this generally comes a change in practice. Most of the advances in how we manage major trauma have come from the arena of war. The MASH units of the Korean conflict taught us that initiating treatment early, in the field, saves lives. The ultimate progression of that concept has been the development of robotic surgery, bringing high level expertise to the field so that skilled intervention can be effected at the earliest possible opportunity. The fact that this can be achieved using robotic technology makes it feasible for a highly skilled surgeon located in some central site to treat multiple injuries in separate locations.

The types of injury seen in war also lead to changes in practice. Plastic surgery, as we know it today, was born during the First World War. Sir Harold Gillies (Fig. 1.4) developed techniques for facial reconstruction initially at Aldershot and later at the Queen's Hospital in Sidcup, Kent. (It later became Queen Mary's Hospital.) His innovative solutions for some of the injuries he saw led to the development of modern plastic surgery. During the Second World War, the Plastic Surgery Unit at the Queen Victoria Hospital in East Grinstead, headed by Sir Archibald McIndoe (Gillies' cousin) (Fig. 1.5) became famous for treating severely burned airmen. This surgery was so experimental that McIndoe's patients formed a club known as the Guinea Pig Club. The club was initially formed as a drinking club and its membership was made up of injured airmen in the hospital as well as the surgeons and

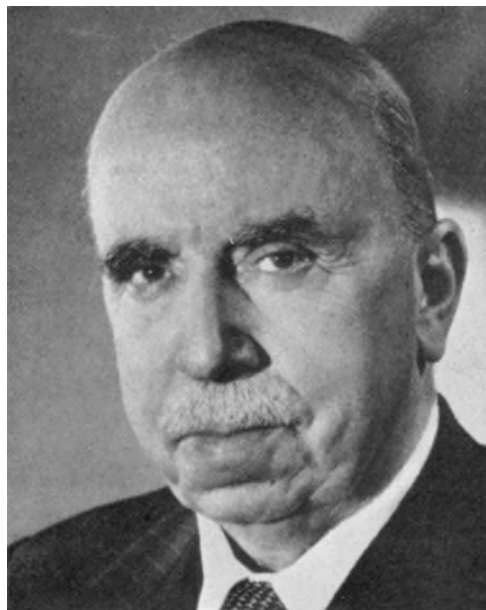


Fig. 1.4 Sir Harold Gillies.



Fig. 1.5 Sir Archibald McIndoe. (Courtesy of Blond McIndoe Research Foundation, registered charity no. 1106240.)

anesthesiologists who treated them. Airmen had to have gone through a minimum of 10 surgical procedures before being eligible for membership in the club. By the end of the war the club had 649 members. The club itself was socially innovative because McIndoe conceived it as a way of integrating injured airmen back into society. He convinced some of the local families in East Grinstead to accept his patients as guests and other residents to treat them as normally as possible. It was very successful and East Grinstead became known as “the town that doesn’t stare”.

Innovation and development in other spheres has also changed the face of plastic surgery and brought further reconstructive challenges to surgeons. For example, the development of effective body armor has led to an increase in the types of injuries we see in the unprotected areas such as the limbs and the head and neck. It is not that these injuries didn’t occur before. It is simply that before the military had effective body armor, soldiers were dying of their injuries and we did not have to deal with their devastating facial or extremity injuries. Limb amputations are surprisingly common. In the US it is estimated that there are 10 000 new upper limb amputees every year. This has led to the development of innovative prosthetics as well as novel techniques to power these prosthetics. Use of myoelectric technology has led to innovations in the surgical approach to amputations and amputation stumps.^{24,25} It is likely that VCA (Ch. 32)) will change the reconstructive landscape for these devastating injuries and we are already seeing that in the upper limb.

Principles of innovation

I mentioned that innovations are based on principles. What are those principles and on what are they based? Obviously the specific principles will depend on the area under study. The principles on which innovation are based will be different for plastic surgeons as compared to gastrointestinal surgeons, for example. Central to everything and what I consider the core of plastic surgery is a detailed knowledge of anatomy. As

a specialty and in general, plastic surgeons have a more detailed knowledge of anatomy than any other specialty. Of course the cardiac surgeon knows the heart better than anyone and the orthopedist knows his bones better than anyone but neither of these specialties are likely to be in each other’s domain very often. Yet the plastic surgeon is frequently asked to cover exposed fractures or to provide vascularized cover for an infected sternotomy wound. Neither of these tasks is possible without a detailed knowledge of the anatomy of the region. Regardless of the area of subspecialty practice one is in, whether it is cosmetic surgery or hand surgery, a detailed knowledge of anatomy is the most important core understanding that is required to do the job well.

To drill down and define what is the single element of anatomic knowledge that is most vital to us, the answer would have to be vascular anatomy. Because so much of what we do involves the rearrangement of tissue, either locally, regionally or from afar, we have to know what keeps that tissue alive and we have to preserve that element. It is interesting to look at the advances that have been made in plastic surgery over the past 50 years. Many of them are directly related to a better knowledge of vascular anatomy. The most tangible of these is the development of flap surgery. We have come from an era when all flaps were random, to the present time when we know not only which blood vessel is supplying our flap but how much of that tissue is being perfused by that blood vessel. Innovations in imaging technology allow us the luxury of a roadmap to the vascular anatomy of our planned reconstruction using CT and/or MRI technology.^{26–28} Even better, we have a surgical GPS that allows us to visualize perfusion in real time using indocyanine green.²⁹ Technical advances allow us to transfer the tissue and perform a microvascular anastomosis to restore its blood supply. However it goes beyond that. We can also restore function, sometimes using microsurgical techniques, other times, once again, utilizing our knowledge of anatomy, by robbing Peter to pay Paul. Tendon transfers, for example, have long been a technique for restoring function to a compromised limb.^{30–32} More recently, nerve transfers have been utilized and are proving to be a valuable addition to our reconstructive armamentarium.³² These are all examples of innovation, describing a new solution to an otherwise insoluble problem.

We have also combined our knowledge of vascular anatomy with our knowledge of genetic engineering. Using genetic engineering we can program cells to perform certain tasks. We can suppress certain functions, stimulate others; in other words we can manipulate cells. This is a very powerful science and has potential applications across all of medicine. The process of transfection, whereby DNA or RNA is introduced into cells to modify gene expression, is widely used in molecular research. Geoff Gurtner, Editor of this volume of *Plastic Surgery* introduced us to the concept of “biologic brachytherapy”.³³ Using techniques of viral transfection, he has been able to design flaps that not only close a surgical defect but introduce a therapeutic element to the reconstruction by having the flap produce peptides appropriate to the disease entity being treated, producing probiotics for infected wounds, or antiangiogenic peptides for oncologic reconstructions. This innovative approach combines the best of plastic surgery with the best of genetic engineering to provide a new and better solution to an existing clinical problem. Biologic brachytherapy represents the melding of anatomic knowledge



Fig. 1.6 Dr. Wayne Morrison.

with tissue engineering principles and is a very exciting development.

The concept of flap prefabrication is another imaginative way of providing a better solution to a clinical problem.³⁴ Using these techniques, the most appropriate reconstructive construct can be assembled prior to the definitive reconstruction. While flap prefabrication is an elegant approach to a complex problem, it demands a high level of expertise, imagination and an innovative outlook. It also demands multiple stages and increased time to complete the reconstruction. In some disease states, such a delay may not be feasible. Engineering body parts is yet another approach that is currently being developed. Wayne Morrison (Fig. 1.6), working in the Bernard O'Brien Institute in Melbourne, has been able to grow functioning cardiac muscle³⁵ as well as functioning islet cells.³⁶ He continues to work on various matrix types to produce vascularized tissue chambers in which different cell types can be grown and vascularized. The ultimate aim is to produce clinically viable engineered organ parts.³⁷ This introduces the concept of “spare-parts” surgery, something that, while still not a reality, is no longer the stuff of science fiction.

The concept of making new tissue constructs is not new and is the basis, for example, of bone distraction and tissue expansion. Tissue expansion has been around since the 1980s. In fact, like many things in medicine, it was originally described long before that,³⁸ but was only popularized in the 1980s.³⁹ It has become one of the standard ways to reconstruct a breast following mastectomy and, of course, it has multiple other uses. When first introduced by Radovan, like many innovations, it was considered with a great deal of skepticism. Unfortunately Radovan did not live to see his idea become widely accepted.

Innovation also involves the application of established techniques in new areas. Bone distraction is an example that was cited already. Devised by Ilizarov for the treatment of long bones, the technique has been adapted to the craniofacial skeleton. The applications of bone distraction in plastic surgery are more recent. Popularized by McCarthy,⁴⁰ bone distraction has changed the practice of craniofacial surgery, minimizing the extent of surgery required to treat certain conditions while improving outcomes. Such developments occur all the time and sometimes there is a disconnect between the development of the original idea and its ultimate application. An example of this is the Brava bra. This was first developed as a means of achieving breast augmentation non-surgically.⁴¹ Applying a

vacuum to the breast caused swelling and enlargement. This was somewhat of a transitory enlargement but, nevertheless, an enlargement. Several other innovations led to a rethinking of what was happening with the Brava system and ultimately led to a very innovative approach to breast reconstruction that is still in the initial stage of skeptical interest but that may well become an established technique. This association of ideas is often how innovation works. What were these different ideas? Each in its own right is a major innovation.

The first is fat grafting. This is an old idea and one with a checkered history. Dermal fat grafts have long been an accepted method of correcting small contour defects. Attempts at engrafting larger fat deposits have generally been unsuccessful. The concept of fat injection as a means of engrafting fat is another idea that was greeted with skepticism until Coleman and others showed us that it does work when the fat is deposited in small aliquots with a fine cannula.^{37,42,43} This technique is now widely practiced in both aesthetic and reconstructive arenas and has become an invaluable addition to our armamentarium.

The second innovation is tissue expansion. Though tissue expansion has been around for a long time, we have thought of it in terms of internal expansion, i.e. expansion produced by the implantation of an expanding device. The suction system used by the Brava bra introduces us to the concept of external expansion, i.e. expansion caused by external forces, the application of a vacuum to the skin.

The third innovation is that of vacuum-assisted closure, the VAC system. This is an idea so simple that we all wish we had thought of it. However, as with many things in medicine, it is not as simple as it first appears. Not only, it appears, does the VAC mechanically remove debris and exudate from the wound, but it also promotes angiogenesis and cell proliferation.^{44–46}

Putting all these concepts together, Khouri has developed a system for both breast reconstruction as well as breast augmentation, which uses the Brava system, married to the structural fat-grafting concept, whereby the external expansion induced by the Brava vacuum produces edema, angiogenesis and cell proliferation that permits larger volumes of fat to be deposited in a favorable matrix, thereby increasing graft take and fat retention. To date, the results of this approach are remarkable. Undoubtedly there are many unanswered questions and here, once again, we have an example of an innovation that has already found clinical application but that requires extensive research to elucidate the mechanism of the clinical picture we are seeing.

Fat grafting, as well as providing a clinical solution to many problems, both aesthetic and reconstructive, has also engaged our curiosity in another area – that of stem cell research. This again represents an association of ideas from disparate fields. Many of the changes we see as a result of fat grafting are not readily explained by the injection of fat alone. As an example, it has been reported that many of the skin changes associated with irradiation seem to be reversed when fat is injected into, for example, a breast defect resulting from lumpectomy and irradiation.⁴⁷ Why should this be? The answer, stem cells, may be a simplistic solution to explain something we don't understand. The answer may also be our introduction into a whole new area of development for plastic surgery. Of course, as we've seen before, not only does this innovation (fat grafting) solve a clinical problem, it raises

numerous questions and opens the door to new areas of research and quite likely to even newer innovations.

External influences and innovation

In order to achieve some of our surgical results we rely not only on our own expertise as surgeons, we also rely on our tools, our instruments and devices. Microsurgery could not have developed without the development of the operating microscope and appropriate instrumentation. One of the biggest barriers to the development of modern microsurgery was the inability to swage an ultrafine suture to a sufficiently small needle. Similarly, the manufacture of implants of any kind demand an expertise that we, as surgeons, do not have. Bioengineers, chemists, physicists and all manner of experts are required to help bring our ideas into clinical practice. None of these developments are possible without the partnership of industry. Of course this is a double-edged sword as it introduces other interests and possible conflicts. Nevertheless, it is a vital part of the development of any specialty.

I've already mentioned how microsuture development led to the development of reconstructive microsurgery. Once it was possible to do microanastomoses, it became possible to replant amputated digits. The new technology spurred the advance of flap surgery and our interest in vascular anatomy was again renewed. This inspired the likes of Mathes and Nahai to elucidate and classify the blood supply of muscles and others to describe new myocutaneous flaps. Ian Taylor started his classic cadaver injection studies that led to the development of the angiosome theory. Later, Isao Koshima and others described perforator flaps and that development and innovation is ongoing.

Craniofacial surgery is another subspecialty area that could not have developed without the help of industry. When Joseph Gruss recognized the importance of internal fixation for the craniofacial skeleton in the early 1980s he was using wires to painstakingly piece together comminuted fractures. This led him and others to the recognition of the concept of facial buttresses and to the development of plating systems for the face. This approach is now standard of care but could not have happened without the expertise of the engineers and implant biologists who worked with surgeons to develop the plating systems and instrumentation that make it all possible. Once again, this is an ongoing process.

Every aspect of plastic surgery has undergone such change and development. In cosmetic surgery we have also seen these changes evolve. In each area, surgeons have developed a better understanding of anatomy and function and developed, with industry, ways to improve and develop the field. Endoscopic techniques were adapted from other areas of practice and applied to the face, and minimally invasive techniques led to the development of barbed sutures and suspension systems. Implant biology has brought us various injectable fillers and broadened the scope of cosmetic surgery in a way that was once unimaginable.

So innovation is a natural consequence of practice. In every sphere people strive to improve things, surgeons to do better operations, anesthesiologists to improve pain control, industry to provide better materials and instruments. These innovations occur in all specialties and, as we have seen, innovation in one specialty can influence how another develops. What

about innovation itself? How can we ensure that innovation is as safe as possible and conducted in some sort of organized fashion and with some form of structure? Do we need such organization and such structure? As I mentioned at the outset, a discussion on the ethics of innovation is beyond the scope of this chapter. However, there are some things that are useful to consider.

Documentation, data gathering and regulation

It is important to document change. If one asks a surgeon how many procedures (s)he has done, the answer is usually a gross exaggeration. Similarly we tend to underestimate our complications. We're not good at remembering stuff though we think we are. It is surprising when one starts to keep a database how sobering it is to see the actual numbers. It's also surprising how much information one can glean and this information is vital if we are to change and improve. Innovation implies change and in times of change it is imperative to document results. How else can one evaluate the effects of the innovation? So documentation and data gathering are important aspects of innovation.

The difficulty with innovation arises in that gray zone between innovation and research. Small changes are easy to effect, large changes more difficult! Most institutions regulate change through the institutional review board (IRB). Regulation is necessary yet it is also restrictive. The IRB process varies from institution to institution but, in general, is getting more and more stringent. This can have a significant effect on the development of medicine as a whole. It is widely believed, for example, that the reason the first heart transplant did not occur in the United States was because of the stringent regulations governing experimental surgery in the US as compared to South Africa where Dr. Christiaan Barnard, an American-trained cardiac surgeon, performed this operation. Institutions also grapple with the dilemma of allowing some degree of innovation, yet controlling quality and risk exposure. The latter is an important consideration for institutions and individuals alike. Apart from protecting the individual and the institution, regulation also introduces and enforces an element of objectivity. When one is involved in developing a theory, an operation, or some sort of change, it is very easy to lose objectivity and that is a serious issue. Regulation enforces objectivity and the difficulty lies in the balance between creativity and objectivity. Just as one can become obsessed with creativity and freedom of expression, however, one can also become obsessed with objectivity and regulation. Finding a balance between the two is sometimes difficult. Added to that is the conflict of interest that is sometimes introduced to the process when a commercial value is associated with the innovation, and particularly when a significant sum may already have been invested in developing it. That introduces the ethics of practice and this subject is covered in Chapter 4.

So we have seen that innovation is an important part of medicine. It is separate from research though often stimulates research. It is as difficult to regulate as it is to define and, at least in some instances, may be stifled by regulation. From all of the innovations I have touched on in this chapter we can see that innovation is vital to the development of medicine in general and to the evolution of plastic surgery in particular.



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History of reconstructive and aesthetic surgery

Riccardo F. Mazzola and Isabella C. Mazzola

SYNOPSIS

- Closure of wounds represents one of the first gestures of reparative surgery.
- History shows that almost every possible local flap has been described in the past and that the ingenuity of plastic surgeons was unlimited.
- The lesson drawn from history reveals that the so-called new flaps are variations of what has already been published.
- We have to be humble and recognize that “nothing is new under the sun.”

Historical definition of plastic surgery

In 1597, the Bolognese Gaspare Tagliacozzi (1545–1597), considered the founder of plastic surgery, gave the following definition of our discipline: plastic surgery is the art devoted to “restore what Nature has given and chance has taken away. The main purpose of this procedure is not the restoration of the original beauty of the face, but rather the rehabilitation of the part in question”,¹ in other terms repair of congenital or acquired defects, restoration of an appearance as close as possible to normality, but also improvement of functional impairment. The term “plastic” comes from the Greek πλαστικός (*plasticós*), moldable.

Origin of plastic surgery

The distant past – the wound as a problem

The ancient origin of plastic surgery relates to the healing of wounds. Management of wounds caused by stones, weapons, arrows, and animal bites goes back millions of years, when primitive humans had to face four major problems: (1) closing posttraumatic defects; (2) bleeding; (3) infection; and (4) pain. Attempts to transform a defect that heals slowly by secondary

intention into one healing quicker by primary intention may well account for the first example of a reparative procedure.

However, this must have been quite complex without appropriate tools, in the presence of hemorrhage and without anesthesia. There is no documentation of stitching of wounds among primitive people.² We may extrapolate from what was reported in ancient Hindu medicine, where wound edges were sewn with simple means like fibers or strips of tendon, or pinned together using insect mandibles. Later, bronze pins were used (Fig. 2.1).

In Ancient Egypt

We are well informed about Egyptian surgery thanks to the Edwin Smith papyrus, the most ancient medical text. The papyrus is a later transcription (about 1650 BC) of an original manuscript dating from the Old Kingdom (between 3000 and 2500 BC). It describes 48 surgical cases, including wounds, fractures, dislocations, sores, and tumors, and suggests their potential management. Fresh wounds were treated conservatively with the application of grease and honey using linen and swabs. Adhesive strips of cloth, stitches or a combination of clamp and stitches were advocated to bring together the margins of the wound. A surgical knife was never mentioned, as wounds already existed in the cases presented.² Treatment of nasal fractures is accurately explained. First, clots should be removed from the inside of the nostrils, then the bony fragments repositioned; two stiff rolls of linen were applied externally “by which the nose is held fast” and finally “two plugs of linen saturated with grease placed into the nostrils.”³

In Mesopotamia

Mesopotamia is the region between the rivers Tigris and Euphrates (now approximately Iraq), cradle of the Sumerian civilization. Medicine was well developed, although strongly influenced by astrology and divination. During excavations of the Nineveh palace, a great library containing more than

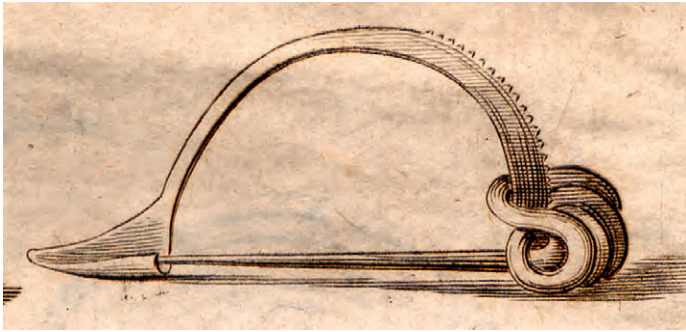


Fig. 2.1 Bronze pin to approximate wound margins. (Reproduced from Rodius J. De Acia Dissertatio. Padua: Frambotto; 1639.)

30 000 clay tablets with cuneiform inscriptions was discovered, 800 of them of a medical nature. They were written about 600 BC, although the text dates from around 2000 BC. A few of them deal with wound healing or congenital anomalies. "If a man is sick with a blow on the cheek, pound together turpentine, tamarisk, daisy, flour of Inninnu [...] mix in milk and beer in a small copper pan; spread on skin and he shall recover."⁴ Another tablet suggests the use of a dressing with oil for an open wound.

Monsters (congenital malformations) had a key role in predicting future events and in determining their course. "When a woman gives birth to an infant [...] whose nostrils are absent, the country will be in affliction, and the house of the man ruined; that has no tongue the house of the man will be ruined; that has no lips affliction will strike the land and the house of the man will be destroyed."⁵ Interestingly, surgery is never mentioned in clay tablets, although surgery was certainly performed. In the King Hammurabi Code,² dating from about 1700 BC, surgical malpractice was recognized with precise laws: "If a physician carried out a major operation on a seignior with a bronze lancet and has caused the seignior's death or he opened the eye socket of a seignior and has destroyed the seignior eye, they shall cut off his hand." "If a physician carried out a major operation on a commoner's slave with a bronze lancet and has caused [his] death, he shall make good slave for slave."

In India

In the Samhita, a Sanskrit text on surgery attributed to Sushruta and possibly dating 600 BC, the description of several reconstructive procedures related to the face are discussed. In particular, management of eyelid anomalies like entropion, trichiasis, or ingrown eyelashes and repair of the nose is reported. Certain Indian populations had the habit of cutting the nose of adulterers, thieves and prisoners of war as a sign of humiliation. In an attempt to improve this terrible disfigurement, surgeons invented different solutions over the centuries.

Repair of the nose was carried out by the Koomas, a low caste of priests, or, according to others, a guild of potters. Local flaps, outlined in the cheek, were used, and accurate description of blunt (*yantra*) and sharp (*sastra*) instruments to perform nasal reconstruction was supplied.⁶

When was the forehead skin used? There is no mention of it. In the second half of the 17th century, the Venetian

adventurer Nicolò Manuzzi (1639–1717) wrote a manuscript about the Moghul empire in which an account of forehead rhinoplasty is supplied. Regrettably the manuscript, kept in the Marciana Library in Venice, was not published until 1907.⁷ Information on the forehead flap in nasal reconstruction only reached the western world at the end of the 18th century, thanks to a letter signed BL, addressed to Mr. Urban, editor of the *Gentleman's Magazine*, and published in October 1794 (Fig. 2.2).⁸

A friend of mine has transmitted to me, from the East Indies, the following very curious and, in Europe, I believe unknown surgical operation, which has long been practiced in India with success; namely, affixing a new nose on a man's face.

There follows the accurate description of the two-step procedure carried out on Cowasjee, a bullock driver of the English



Fig. 2.2 Indian forehead flap nasal reconstruction. (Reproduced from BL. Letter to the editor. *Gentleman's Magazine*. 1794;64:891–892.)

army, who fell under the disfavor of Tippoo Sultan, and had his nose amputated. It demonstrated the high level of surgery reached by the Indians in performing an operation, without anesthesia, in a very similar way to what we do nowadays.

In Greece

Greek medicine was influenced by Hippocrates, the greatest physician of his time. Historians consider that Hippocrates was born in the island of Kos around the year 460 BC, and probably trained in medicine at the Asklepieion of Kos. In ancient Greece and Rome, the Asklepieion (Latin: *aesculapīum*) was a healing temple, sacred to Asklepios, the Greek god of medicine. Hippocrates rejected the views of his time that illness was due to supernatural influence, possession of evil spirits, or disfavor of the gods. He based his medical practice on the direct observation of disease and on an analysis of the human body, introducing scientific methods into medicine. Hippocrates taught and practiced medicine throughout his life, traveling in various Greek regions. He established the Great School of Medicine on the isle of Kos. He probably died in Larissa (Greece) at the age of 83 or 90.

About 70 medical treatises, assembled during the Alexandrian era (third century AD), were attributed to Hippocrates. They form the so-called *Corpus Hippocraticum*. Whether Hippocrates himself is the author of the *Corpus* and these works are authentic has been the matter of great dispute and controversy.⁹ The *Corpus* contains manuals, lectures, research, philosophical thoughts, and essays on different topics of medicine, without any logical order and even with significant contradictions among them. The works of Hippocrates were true best-sellers, reprinted numerous times over the centuries. The first printed edition of the *Opera omnia* (Complete Works) was issued in Latin in Rome in 1525, and in Greek in Venice in 1526 by the Aldine Press.

The surgical knowledge of Hippocrates was vast. He used cauterization for the management of raw surfaces, reduced malunited fractures, and practiced cranial trephination to evacuate hematomas.

In Rome

In Rome, surgery was well developed, at least judging from the rather sophisticated bronze instruments discovered in Pompei and now kept at Naples National Museum. Many were stored in traveling kits to be used by surgeons for emergency or in the battlefields.

The two most representative figures of Roman medicine were Celsus and Galen.

Aulus Cornelius Celsus (25 BC–50 AD) was probably not a physician, but a writer from a noble family and the author, in about 30 AD, of *De Medicina* (On Medicine) in eight volumes. In book seven, chapter nine, vessel ligation and lithotomy as well as lip closure (cleft lip or lip tumor) by means of flaps are reported. It is explained how “defects of the ears, lips and nose can be cured” (*curta in auribus, labrisque ac naribus, quomodo sarciri et curare possint*), followed by a description of wound closure by advancement flap.¹⁰ “The defect should be converted into a square (*in quadratum redigere*). Then, from the inner angles transverse incisions are made (*lineas transversas incidere*), so that the part on one side is fully divided from that on the opposite side.” “After that, the tissues which have been

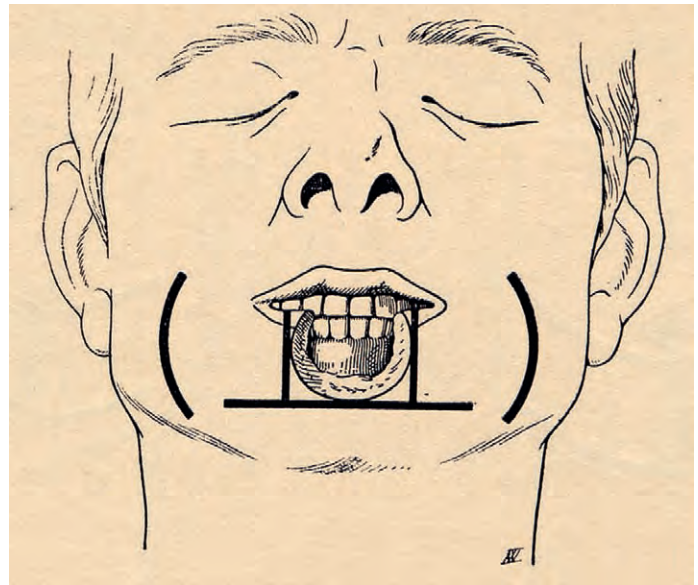


Fig. 2.3 Lip repair according to Celsus. (Reproduced from Nélaton C, Ombredanne L. *Les Autoplasties*. Paris: Steinheil; 1907.)

undermined, are brought together” (*in unum adducere*). “If this is not possible two additional semilunar incisions are made at some distance from the original (*ultra lineas, quas ante fecimus, alias duas lunatas et ad piagam conversas immittere*), but only sectioning the outer skin. [...] These latter incisions enable the parts to be easily brought together without using any traction” (Fig. 2.3). Celsus holds a key role in the history of plastic surgery, as he is considered the earliest writer on this particular topic. He introduced the four cardinal signs of acute inflammation, “redness and swelling with heat and pain” (*rubor et tumor, cum calore et dolore*). A copy of Celsus’s manuscript was discovered in Milan in 1443, and printed for the first time in 1478 in Florence.¹¹ *De Medicina* went through more than 50 editions.

Claudius Galen (c. 129–201 AD) was born in Pergamon (Turkey), studied medicine at the Asklepieion (see above) in his native city and moved to Rome. He wrote about head traumas, techniques of trephination for evacuating hematomas and various types of bandaging. An excellent anatomist, he described more than 300 muscles, the seven pairs of cranial nerves and contributed to neurology, demonstrating that nerves arise from the brain or spinal cord. He observed that section of the laryngeal nerve resulted in dysphonia. For management of wounds he used sutures and cautery. Numerous works of Galen were lost, but 82 survived. Originally written in Greek, many were translated into Arabic and Latin. Galen’s *Opera* was first printed in Latin in Venice in 1490 and in Greek in Venice in 1525 by the Aldine Press.

Plastic surgery after the decline of the Roman Empire

Byzantine surgery

Oribasius (325–403 AD) wrote a collection of medical texts entitled *Synagogae Medicae* in which reconstructive procedures for cheek, nose, ears, and eyebrow defects are described.¹²

Paulus of Aegina (625–690 AD), surgeon and obstetrician, was the author of a medical encyclopedia (*Epitome*) in seven volumes. In book 6, which deals with surgery, a description of tracheotomy, tonsillectomy, ectropion, upper eyelid retraction and lip repair is supplied.^{13,14} “Defects [Greek, *colobomata*] of the lips and ears are treated in this way. First the skin is freed on the underside. Then the edges of the wound are brought together and the callosity is removed. Finally, stitches holding the margins into position are applied.” This technique closely resembles that of Celsus.

The Middle Ages

Arabian surgery

Arabian medical writers came from different nations, such as Persia, Syria, and Spain. Their only common denominator was the language. The most representative figure was Abū-l-Qāsim or Albucasis (c. 936–1013 AD), whose famous treatise, *Al Tasrif* (*On Surgery*), was translated into Latin and first published in 1500. It included more than 200 illustrations of surgical instruments, such as tongue depressor, tooth extractor, hooks, and cauteries, most invented by Albucasis himself, with an explanation of their use.¹⁵ Like most Arabian surgeons, Albucasis was a proponent of cautery, for different clinical applications and the management of wounds and cleft lip. He was the first to use a syringe with a piston.

The rise of the universities

The founding of the universities is one of the most important events in the Middle Age and a key factor in the development of modern culture. Originally, *universitas* denoted an aggregation of masters (*magistri*), students, or both, and the primary goal was teaching philosophy and theology. Lessons were practiced in the house of the masters or in small rooms. Students sat on the floor, whereas the professor was in the chair. The oldest university, at least in Europe, was Bologna, established in 1088, followed by Paris, Oxford, and Montpellier. In Bologna medicine was taught and cadaver dissection was accepted, thus significantly contributing to the development of the study of anatomy. Mondino de’ Luzzi (1270–1326) was the first anatomist to lecture directly in front of the cadaver (Fig. 2.4). As anatomists were also surgeons, such as Henry of Mondeville (1260–1320) or Guy of Chauliac (1300–1368), surgery was part of the teaching program of anatomy.

The discovery of printing

The invention of printing around 1440 by Gutenberg spread medical knowledge and considerably enlarged the libraries of universities and monasteries.

The first printed textbook on surgery was *La Ciroxia* (*On Surgery*), by William of Saliceto (1210–1277), issued in Venice in 1474. This text has particular relevance in the history of surgery, because it reintroduced the use of the surgical knife to replace cautery, strongly advocated by Arabian surgeons. The first printed textbook on anatomy was *Anatomia* by Mondino de’ Luzzi, issued in Padua about 1476, which remained the reference text for numerous years. The printed works of Hippocrates, Galen, Celsus and Arabian writers played a key role in educating medical students.



Fig. 2.4 Mondino in the chair supervising a cadaver dissection. (Reproduced from Ketham J. Fasciculus de Medicina. Venice: Gregorio de’ Gregorii; 1493.)

The Renaissance

Renaissance surgery

The most celebrated surgeon of the Renaissance was the Frenchman Ambroise Paré (1510–1590) (Fig. 2.5). A humble but very talented barber-surgeon, Paré amassed considerable experience from his tireless work in the battlefields. At that time, gunshot wounds were considered poisoned and barbarically cauterized either with red-hot iron, or with boiling oil poured directly into the wound. On the contrary, Paré used simple dressings and soothing ointment made of egg yolk, oil of roses and turpentine with great benefit for the soldiers. The conclusion was that less invasive methods were far superior to the traditional ones. In 1545 he published his observation in *La Méthode de traicter les playes...* (*The Method of Treating Wounds...*). Paré’s works were collected in a single folio volume, “*Les Oeuvres*”, first published at Paris in 1575 and dedicated to Henry II, King of France.¹⁶ Paré’s contributions to plastic surgery were significant. He showed the first image of a cleft lip suture in medical literature (Fig. 2.6). To facilitate healing avoiding potential wound breakdown and reducing the risk of unpleasant wide scar formation on the face, he applied adhesive and fastened the wound margins (Fig. 2.7).



Fig. 2.5 Portrait of Ambroise Paré (1510–1590).

He described and illustrated a vast number of congenital malformations, some real and others the result of fantasy, the so-called monstrosities.

The year 1583 marks a great breakthrough in ophthalmology and eyelid surgery with "*Ophthalmodouleia, das ist Augendienst*" (Ophthalmodouleia, or the Service of the Eyes) by Georg Bartisch (1535–1607), oculist to the Elector August of Saxony.¹⁷ The book constitutes the first comprehensive treatise on the care and management of the diseases of eye and adnexa and is embellished by dozens of detailed anatomical images of the eye, eyelids and brain, as well as of surgical instruments. Besides this, it includes the first clinical illustration of blepharochalasis and baggy eyelid (Fig. 2.8) and the report of an original technique for surgical excision of the overhanging skin fold above the tarsus for correcting blepharochalasis, using a curved clamp in the form of a guillotine (Fig. 2.9).

The beginning of plastic surgery is usually associated with *De Curtorum Chirurgia per Insitionem* (On the Surgery of Injuries by Grafting),¹⁸ published in Venice in 1597, by Gaspare Tagliacozzi (1544–1599), Professor of Surgery at Bologna University, in which the procedure for nasal reconstruction is shown step by step and skillfully illustrated. The instruments necessary for the operation are presented first, followed by the indications, flap outlining on the arm, flap inset, the bandage necessary to secure the arm into position, resection of the vascular pedicle, final result, as well as the different clinical

applications of the technique for lip and ear defects (Fig. 2.10). The book was well received and reprinted in a pocket edition at Frankfurt the following year, directed specifically at military surgeons who were often confronted with the problems of nasal repair in the battlefields.

But when did nasal reconstruction start in the western world and from whom did Tagliacozzi learn the technique?

The operation was performed by members of the Branca family from Catania (Sicily). Gustavo (early 15th century) used skin taken from the cheek. His son, Antonio, made considerable improvements to the operation. He selected the arm as the donor site, to avoid further scars on the face. About 1460, at Antonio's death, the Branca method, which was kept as a family secret and passed on by word of mouth, was discontinued in Sicily. It was resumed by Vincenzo Vianeo in Calabria (southern Italy). His sons Pietro (about 1510–1571) and Paolo (about 1505–1560) established a flourishing clinic for rhinoplasty in Tropea (Calabria). Evidence of their reconstructive work comes from the Bolognese army surgeon Leonardo Fioravanti (1517–1588), who assisted in Vianeo's operations and issued a detailed report in *Il Tesoro della Vita Humana* (Treasure of Human Life) issued in Venice in 1570.¹⁹

I moved to Tropea where at that time there were two brothers Pietro and Paolo, who made a nose for anyone who had lost his by some accident [...]. I went every day to the house of these



Fig. 2.6 Cleft lip repair. (Reproduced from Paré A. *Les Oeuvres*. Paris: Buon; 1575.)



Fig. 2.7 Facial wound suture. A piece of linen is stitched to the skin to facilitate wound edge approximation. (Reproduced from Paré A. *Les Oeuvres*. Paris: Buon; 1575.)

surgeons, who had five noses scheduled for repair and when they wanted to perform these operations they called me to watch and I, pretending I had not the courage to look at, I turned my face away, yet my eyes saw perfectly. Thus, I observed the whole secret from top to toe, and learned it.

Then follows the description of the arm flap procedure.

Possibly Fioravanti's book came to the attention of Gaspare Tagliacozzi who successfully applied the technique on some patients and published his famous textbook in 1597. Although Tagliacozzi was not the discoverer of rhinoplasty, and the arm flap operation is now rarely performed, he deserves credit for being the first to make a work of art out of a surgical practice, for systematizing and promulgating nasal reconstruction. He is rightly considered the founder of plastic surgery.



Fig. 2.8 Blepharochalasis and baggy eyelids. (Reproduced from Bartisch G. *Ophthalmoduleia, das is Augendienst*. Dresden: Stöckel; 1583)

The decline of plastic surgery

After Tagliacozzi's death, apart from his pupil G. B. Cortesi (1554–1634), who published a book on nasal reconstruction in 1625,²⁰ the operation, which was difficult to perform, became obsolete for almost two centuries. Sporadic cases were

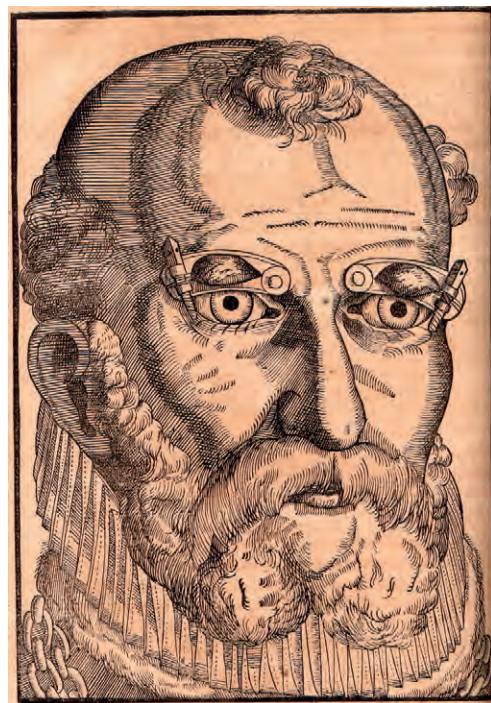


Fig. 2.9 First illustration of blepharochalasis correction. (Reproduced from Bartisch G. *Ophthalmoduleia, das is Augendienst*. Dresden: Stöckel; 1583)

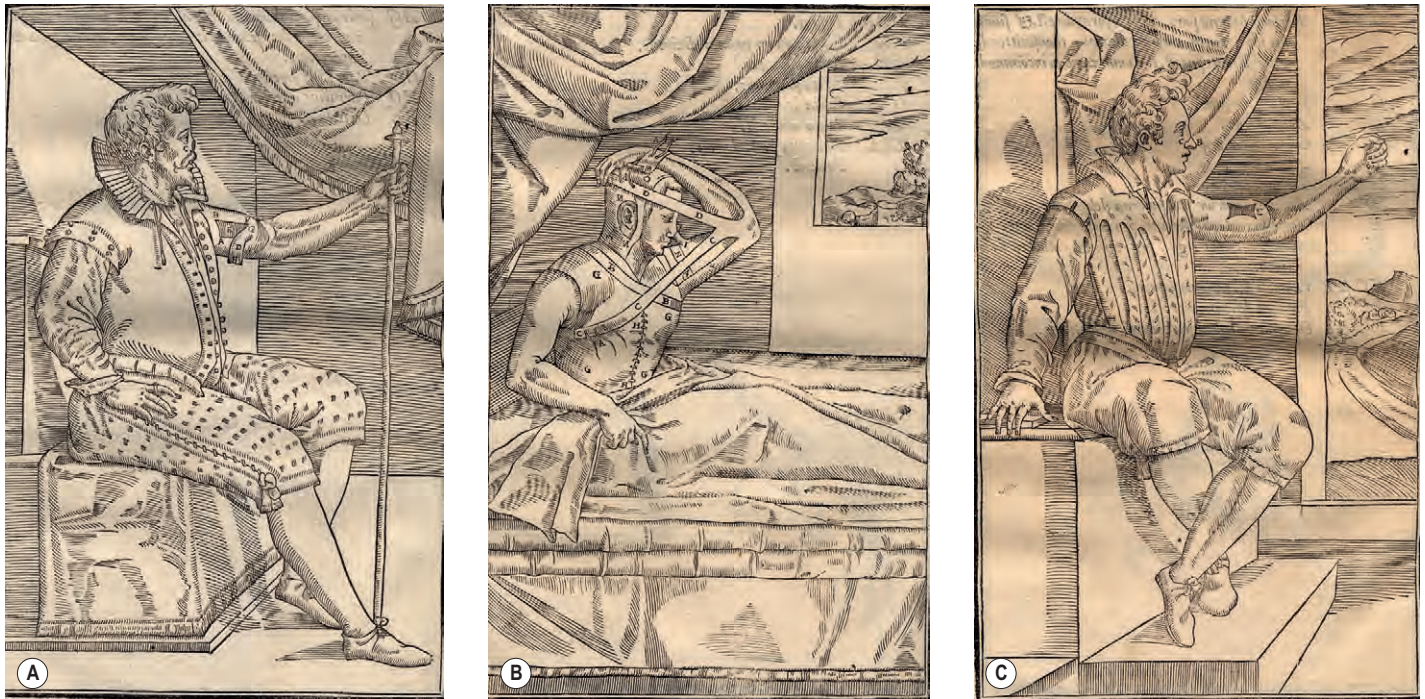


Fig. 2.10 Nasal reconstruction with the arm flap. **(A)** Preoperative view of the patient. The missing nose and flap are outlined. **(B)** The flap sutured into position. **(C)** Final result. (Reproduced from Tagliacozzi G. *De Curtorum Chirurgia per Insitionem*. Venice: Bindoni; 1597.)

reported in 17th- or 18th-century literature. Instead of recommending autologous tissue for restoring a missing nose, surgeons like Fallopio (1523–1562), Heister (1683–1758), Camper (1722–1789), and others advocated the application of a prosthesis, convinced that noses made out of wood or silver were far superior to those of skin.

The rebirth of plastic surgery

The 1794 letter to the editor of the *Gentleman's Magazine* (see above) holds a key position in the revival of plastic surgery. The English surgeon Joseph Constantine Carpue (1764–1846) read it and made practical and successful use of its contents. In 1814, he carried out the first forehead flap rhinoplasty of modern time at St. Bartholomew's Hospital, London, on an officer of His Majesty's Army, who had his nose amputated during a battle. The operation lasted 35 minutes, "it was no child's play, extremely painful – the officer said – but it was no use complaining." At the end he exclaimed: "my God, there is a nose!"

In 1816, Carpue issued an account of nasal reconstruction, which marks the prelude to the rebirth of modern plastic surgery (Fig. 2.11).²¹

The 19th century

The golden age of plastic surgery

Carpue's work was immediately translated into German, and Carl Ferdinand von Gräfe (1787–1840), Professor of Surgery at Berlin University, promptly initiated the operation. In 1818,

he published *Rhinoplastik oder die Kunst den Verlust der Nase organisch zu ersetzen* (*Rhinoplasty: or the Art of Reconstructing the Nose*), where he compared the Italian and Indian procedures.²² Von Gräfe supported the arm flap, as he was unhappy about forehead donor site scar morbidity.

The publications of Carpue and von Gräfe stimulated the interest of European surgeons to carry out nasal and other reconstructions. In Germany, Johann F. Dieffenbach (1794–1847), head of surgery at La Charité Hospital in Berlin, performed rhinoplasty, facial restorations, cleft lip and palate repairs. He reported his contributions in *Chirurgische Erfahrungen* (*Surgical Experiences*), issued in 1829.²³ In France, Jacques Mathieu Delpach (1777–1832), chief surgeon at Montpellier, wrote *Chirurgie Clinique de Montpellier* in 1828, with a detailed section on rhinoplasty.²⁴ Outstanding works on the rediscovered art were presented by Pancoast (1805–1882)²⁵ in the US, Balassa (1814–1868)²⁶ in Hungary, and Sabattini (1810–1864)²⁷ in Italy. A review of the state of the art of nasal reconstruction in Europe in the mid 19th century was published by Nélaton and Ombredanne in 1904,²⁸ and more recently by McDowell,²⁹ Rogers,³⁰ and Mazzola.³¹

With the advent of anesthesia (1846) and the possibility of closing the donor site primarily, leaving a scar that was often unnoticeable, forehead rhinoplasty became the procedure of choice due to its simplicity, good color match, and excellent results.

The first attempt to close a cleft palate goes back to the second decade of the 19th century. The priority is shared between Carl Ferdinand von Gräfe³² and Philibert Roux (1780–1854) from France.³³ However, the greatest advance was made in 1862 by Bernard von Langenbeck (1810–1887), who outlined two mucoperichondrial flaps obtaining a more reliable closure.³⁴ Refinements in cleft lip repair were published

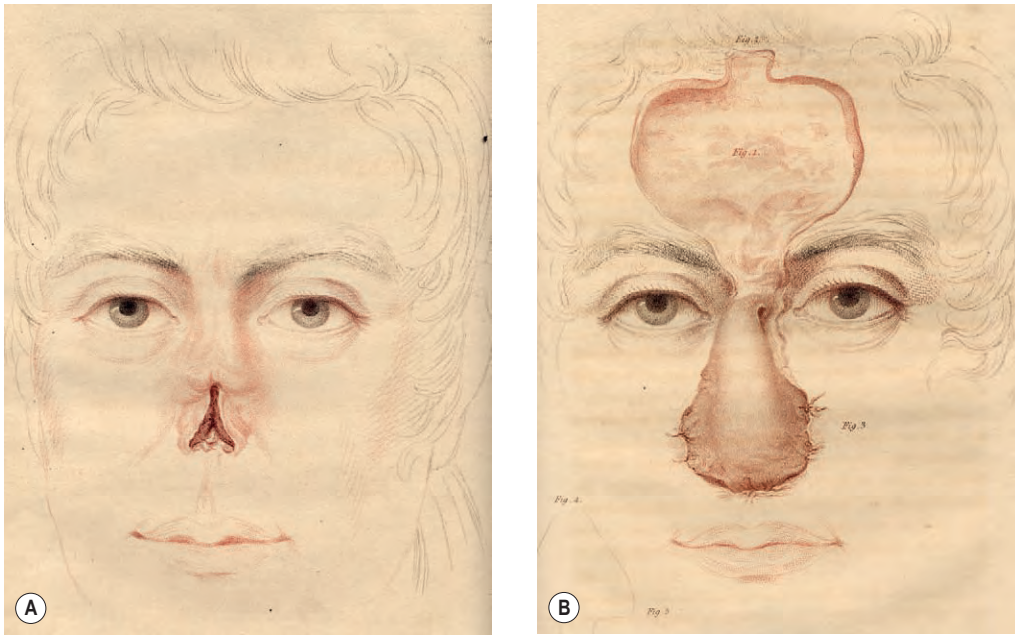


Fig. 2.11 Nasal reconstruction with the forehead flap. **(A)** Preoperative view. **(B)** The flap transposed into position. (Reproduced from Carpie JC. An Account of Two Successful Operations for Restoring a Lost Nose from the Integuments of the Forehead, in the Case of Two Officers of his Majesty's Army. London: Longman, Hurst; 1816.)

by the Frenchmen Joseph Malgaigne (1806–1865)³⁵ and Germanicus Mirault (1796–1879) in 1844.³⁶

Reconstructive procedures for lip³⁷ were reported by Pietro Sabattini in 1838, using the lip switch technique^{27,38} (Fig. 2.12), and by Victor von Bruns (1812–1883) in 1857, using double lateral flaps for oral sphincter restoration³⁹ (Fig. 2.13), whereas eyelid repair was reported by Johann Fricke (1790–1841) in 1829, who described a pedicled skin flap from the ipsilateral temple or cheek region to correct upper or lower eyelid defects, respectively⁴⁰ (Fig. 2.14).

One of the greatest advances in 19th-century surgery was the demonstration that a piece of skin, fully separated from its original site, might survive when transplanted to another part of the body to cover a granulating raw surface.⁴¹ This

became possible through the pioneering work of Giuseppe Baronio (1758–1811) from Milan, who performed the first autologous skin graft in a ram in 1804 (Fig. 2.15).^{42,43} Sixty-five years later, Jacques Reverdin (1842–1929) carried out the first successful epidermic graft on a human being at Hôpital Necker in Paris, opening a new era in wound-healing management.⁴⁴ The route for skin grafting was traced. A few years later, Louis Ollier (1830–1900) transferred a large piece of split-thickness skin, which included the superficial layers and underlying dermis.⁴⁵ Carl Thiersch (1822–1895)⁴⁶ and John R Wolfe (1824–1904)⁴⁷ made further advances in the procedure. In the late 1800s, skin grafting became the preferred solution for the management of chronic and granulating wounds.

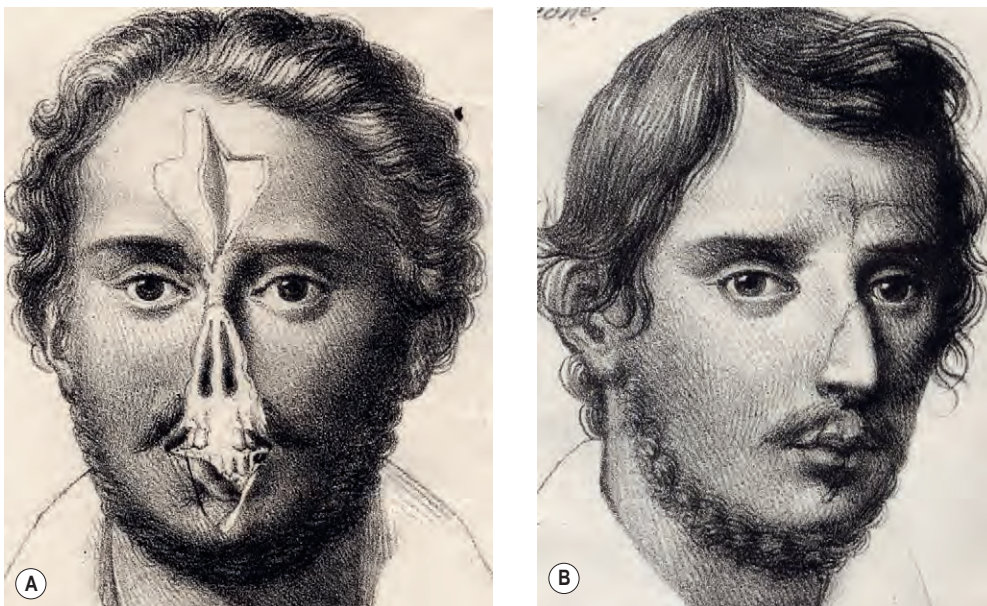


Fig. 2.12 The lip switch technique for upper lip repair. **(A)** Flap outlining. **(B)** Final result. (Reproduced from Sabattini P. Cenno storico dell'origine e progressi della Rinoplastica e Cheiloplastica seguita dalla descrizione di queste operazioni praticamente eseguite sopra un solo individuo. Bologna: Belle Arti; 1838.)

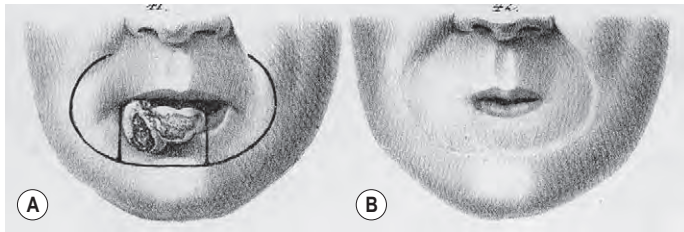


Fig. 2.13 (A,B) The double lateral flaps for lower lip repair. (Reproduced from von Bruns V. *Chirurgischer Atlas*. Tübingen: Laupp; 1857.)

The 20th century

The origin of modern plastic surgery

Trenches played an important role during World War I. Created for shielding purposes, they actually only protected soldiers' lower body and trunk, whereas the head and neck remained exposed to enemy weapons. As they returned home, soldiers with major maxillofacial mutilations found it impossible to step back into society, and this constituted a new social problem. Treatment of these devastating facial wounds urged the development of a new discipline, reconstructive surgery. The first plastic surgeons came from general surgery, otolaryngology, or orthopedics during the first two decades of the 20th century.

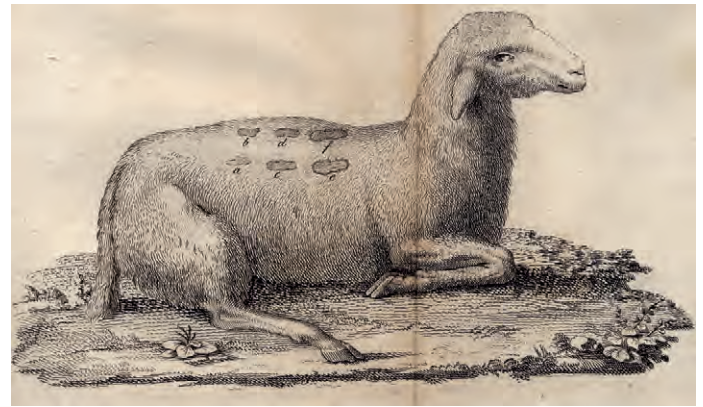


Fig. 2.15 First autologous skin graft in a ram. (Reproduced from Baronio G. *Degli innesti Animali*. Milan: Stamperia del Genio; 1804.)

Associations were created all over the world to help these poor individuals. The most famous was *Les gueules cassées* (The Facial Cripples), founded in France in 1921, by Colonel Picot. In addition to these associations, France, the UK, Germany, Italy, and Czechoslovakia established specialized centers to manage injuries that had never been seen before. The key to success was the cooperation between plastic surgeons, trained in soft-tissue defect management, and oral surgeons, expert in stabilizing bone fractures using dental appliances.

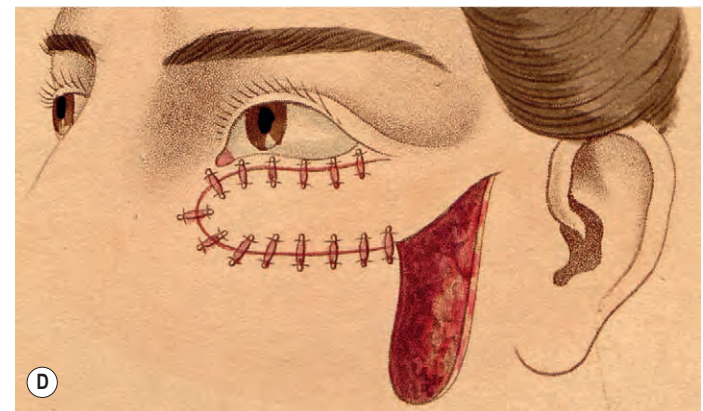
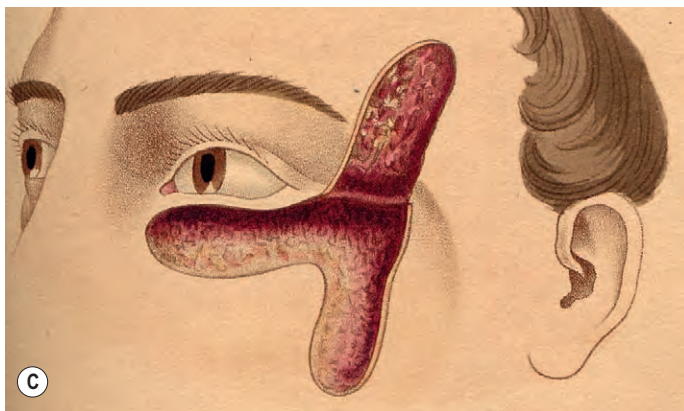


Fig. 2.14 (A–D) Upper and lower eyelid repair with a temporal and cheek flap, respectively, according to Fricke. (Reproduced from Fritze HE, Reich OFG. *Die plastische Chirurgie*. Berlin: Hirschwald; 1845.)

Hippolyte Morestin (1868–1919), who worked with the dentist Charles Auguste Valadier (1873–1931) at Hôpital Val-de-Grâce (Paris), first realized the importance of such a team approach. For this he is considered the pioneer in facial reconstructive surgery.

In 1915, the New Zealand otolaryngologist Harold Gillies (1882–1960), at that time working in France on behalf of the Red Cross, visited Val-de-Grâce military hospital. He was much impressed by the work of Hippolyte Morestin and Valadier pushed him to take care of facial disfigurements. In 1917, upon his return to the UK, Gillies established a center for the management of face and jaw injuries at Queen's Hospital, Sidcup. It became the referral center in Europe. Treatment was provided to British and allied soldiers wounded in the Battle of the Somme (July 1, 1916), where Britain suffered almost 500 000 casualties with an enormous number of dramatic facial mutilations (Fig. 2.16). Gillies operated among a multidisciplinary team with William Fry (1889–1963) and Henry Pickerill (1879–1956) as dental surgeons, and a qualified group of anesthesiologists. He systematized new reconstructive procedures, like the tubed flap, described by the Russian Vladimir Filatov (1875–1956),⁴⁸ which allowed the coverage of large skin defects, but also skin flaps, bone, cartilage, and skin grafts (Fig. 2.17). Gillies reported his experiences in *Plastic Surgery of the Face*, issued in 1920.⁴⁹

In Germany Erich Lexer (1867–1937), one of the founders of maxillofacial surgery, built up a vast experience on the repair of the face, mandible, and eye socket using cartilage, bone, skin, and fat graft. He published a book on reconstructive surgery in 1920.⁵⁰

The Dutch surgeon Johannes Esser (1877–1946) was active at Tempelhof Hospital, Berlin, and in Vienna. Between 1916 and 1918 Esser codified some of the flaps currently used today: cheek rotation⁵¹ (Fig. 2.18), bilobed, island, and arterialized flaps, which he called biological flaps.⁵² In Italy, Gustavo Sanvenero Rosselli (1897–1974) was appointed head of the *Padiglione per i Mutilati del Viso* (Pavilion for Facial Cripples) in Milan (Fig. 2.19). It became a European referral center for reconstructive surgery and was visited by surgeons from all over the world.

Frantisek Burian (1881–1965) headed an important plastic surgery unit in Prague, Czechoslovakia.



Fig. 2.16 Dramatic facial mutilations from World War I. (Reproduced from Pickerill HP. *Facial Surgery*. Edinburgh: Livingstone; 1924.)

In the US the specialty only grew after World War I. Vilray Blair (1871–1955), trained at Sidcup, established the first independent unit in the US for the care of complex maxillofacial injuries at Walter Reed Hospital. Other renowned reconstructive surgeons were Robert Ivy, Truman Brophy, John Staige Davis, and the Armenian Varaztad Kazanjian.

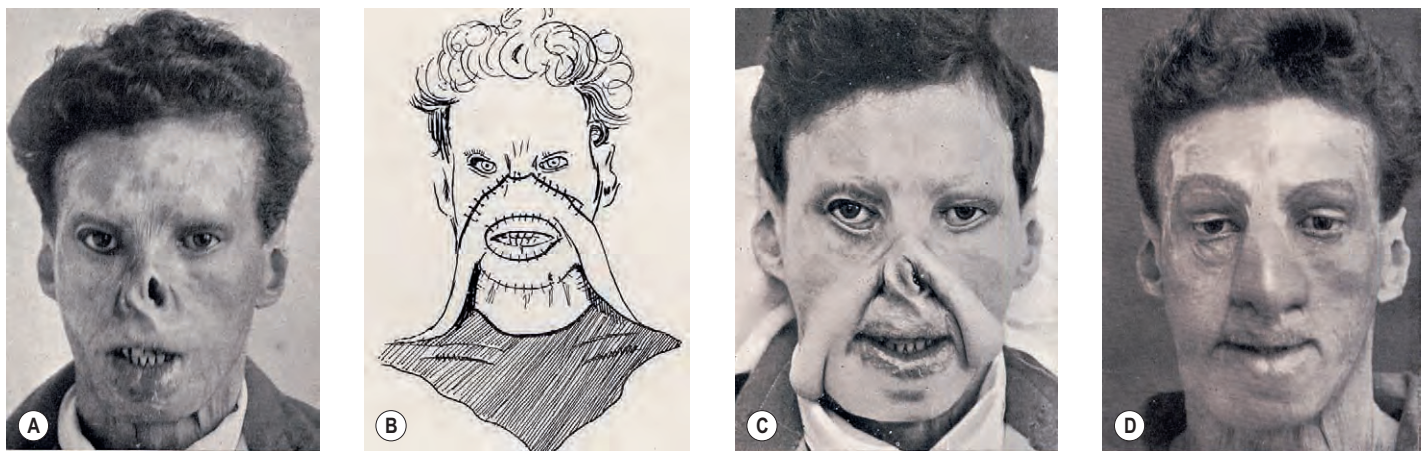


Fig. 2.17 Sequelae of facial burn from World War I. Repair using the tubed flap. (A) Preoperative view of the patient. (B) Outlining of the tubed flap. (C) The flap in position. (D) Final result. (Reproduced from Gillies H. *Plastic Surgery of the Face*. London: Frowde, Hodder and Stoughton; 1920.)

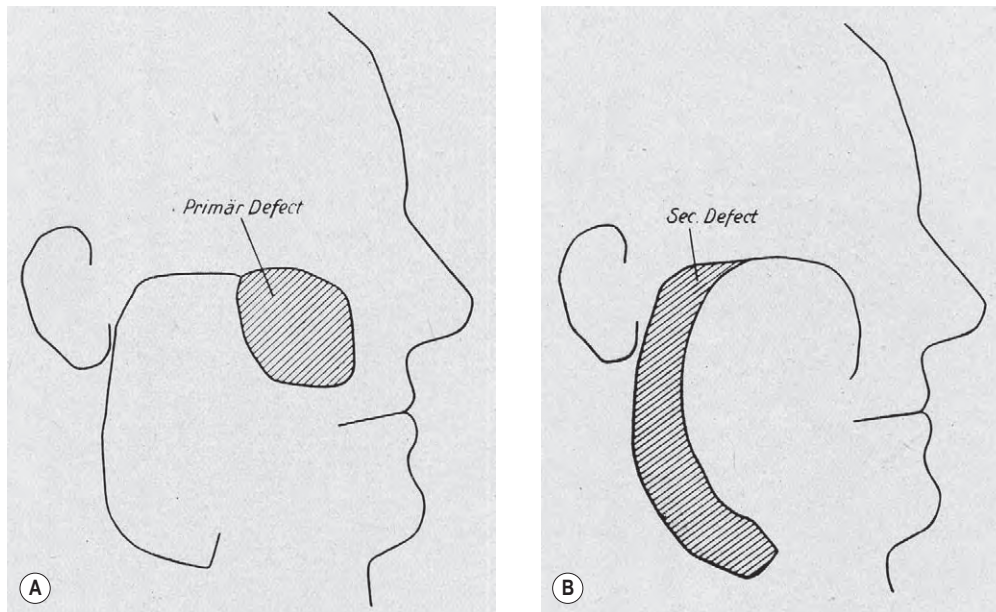


Fig. 2.18 Cheek flap transposition for closing of an orbitopalpebral defect. (Reproduced from Esser JFS. *Die Rotation der Wange*. Leipzig: Vogel; 1918.)

The training programs

By the end of World War I, reconstructive techniques had achieved surprising results. Transfer of skin flaps (tubed or pedicled) and use of grafts (skin, cartilage, bone, fat) became routine procedures. New units were established all over the world. Thus, the need for training programs, where young doctors could become familiar with reparative methods, was essential. Queen's Hospital at Sidcup, headed by Sir Harold Gillies, was probably the most famous for the management of facial injuries. Anesthesia improved considerably thanks to Ivan Magill, who developed nasal and endotracheal intubation. Other training programs in the UK were organized by Sir Archibald McIndoe, Rainsford Mowlem, and Pomfret Kilner.

In Paris, the otorhinolaryngologist Fernand Lemaître (1880–1958) established a residency at the International Clinic of Oto-Rhino-Laryngology and Facio-Maxillary Surgery, having Eastman Sheehan (1885–1951), Professor of Plastic Surgery at Columbia University New York, as course director

(Fig. 2.20). The 2-year fellowship included an intense program of lectures and practical surgical demonstrations. Attendees from various parts of Europe and the US were numerous. Among them was the Italian Gustavo Sanvenero Rosselli, later appointed head of the Plastic Surgery Clinic in Milan. In the US the first training program was organized by Wilray Blair at Washington University in St. Louis.

The birth of the scientific societies

The aim of the scientific societies was to improve the scientific level of the specialty and to defend the public from charlatans. The first society was the American Association of Oral and Plastic Surgeons, established in 1921 by Truman Brophy (1848–1928), who strongly supported close cooperation between oral and plastic surgeons. Initially membership required the MD and DDS degrees.

In Europe, the first society was the Société Française de Chirurgie Réparatrice Plastique et Esthétique, established in 1930 by Charles Clauoué (1897–1957) from Bordeaux and Louis Dartigues (1869–1940) from Paris. It only lasted 2 years.



Fig. 2.19 The Pavilion for Facial Cripples in Milan, headed by G. Sanvenero Rosselli (1897–1974).



Fig. 2.20 Fernand Lemaître and Eastman Sheehan at the International Clinic in Paris, in 1927.



Fig. 2.21 Executive Council members of the Société Européenne de Chirurgie Structive, Brussels, 1936. From left to right: Sir H. Gillies, J. F. S. Esser, M. Coelst, P. Kilner, G. Sanvenero Rosselli.

In 1931, Jacques Maliniak (1889–1976) founded the American Society of Plastic Surgeons.

The first supranational society was the Société Européenne de Chirurgie Structive, created in 1936 by the Belgian Maurice Coelst (1894–1963) (Fig. 2.21), with the aim of gathering annually all those international specialists interested in the new discipline.⁵³ The term *structive* was coined by Johannes Esser, as he considered it more appropriate than “plastic” to emphasize the repairing concept.

In 1937, Vilray Blair organized the American Board to certify real plastic surgeons.

The scientific journals

At the time of the foundation of the American Society (1931), the Belgian Maurice Coelst established and edited the *Revue de Chirurgie Plastique* (Fig. 2.22). The journal, the first one on this topic, played an important role in the history of plastic surgery between the two wars. Thanks to an international editorial board, which included the most prestigious plastic surgeons, the journal published high-quality papers written by Gillies, Maliniak, and Rethi, the proceedings of the American Society of Plastic Surgery and those of the Société Française de Chirurgie Réparatrice Plastique et Esthétique.⁵⁴ Papers appeared in the author’s preferred language and were summarized in English, French, and German.

In 1935, the *Revue de Chirurgie Plastique* changed its name into *Revue de Chirurgie Structive*, becoming the official journal of the Société Européenne de Chirurgie Structive. The *Revue* lasted until the end of 1938 (8 years), when it ceased publication, due to the advent of World War II.

In 1946, the *Plastic and Reconstructive Surgery Journal* was established and Warren B. Davis was appointed as an editor.

The bases for the official recognition of plastic surgery as an independent specialty were settled.

Postwar plastic surgery

Recent history sees an incredible development of new reconstructive procedures, initiated in the 1960s with the recognition of arterialized flaps, continuing with the clinical definition of the cutaneous vascular territories nourished by a single vessel, first identified by Carl Manchot (1866–1932) in 1889⁵⁵ (Fig. 2.23), and culminating with their microvascular transfer.

The application in surgical practice of musculocutaneous flaps, originally described by the Italian Iginio Tansini (1855–1943)⁵⁶ (Fig. 2.24), the introduction of craniofacial techniques, developed in the late 1960s by Paul Tessier (1917–2008),⁵⁷ the systematization of breast reconstruction, the use of fat grafting for numerous aesthetic and reconstructive indications,⁵⁸ and even the most recent face transplantation, constitute further achievements of our specialty.

Aesthetic surgery

The origin

The history of aesthetic surgery begins in 1845, when Johann F. Dieffenbach (1794–1847) described external incisions to reduce large, hanging noses with the dual purpose of modifying the nasolabial angle and decreasing the size of the nose.⁵⁹ No illustration was provided. The same operation was undertaken a few years later by the Latvian surgeon Julius von Szymanowski (1829–1868), who reported it in his “*Operatizij poverchnosti...*” (*Handbook of Operative Surgery*),⁶⁰ showing the illustration of the procedure. The change of the nasolabial angle and the aesthetic goal of the procedure were emphasized.

Correction of prominent ears, performed in 1881 by the New York surgeon Edward Ely (1850–1885) and modifications of nasal appearance are considered among the first purely cosmetic procedures.⁶¹

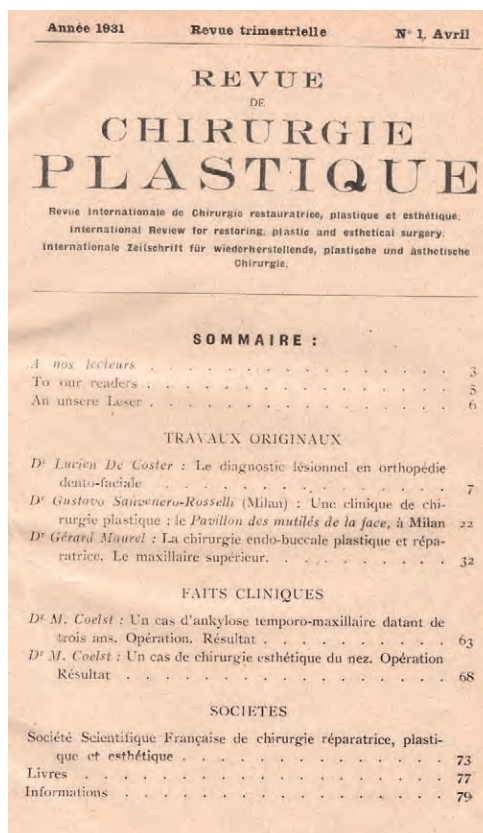


Fig. 2.22 The first issue of the *Revue de Chirurgie Plastique*, established by M. Coelst in 1931.

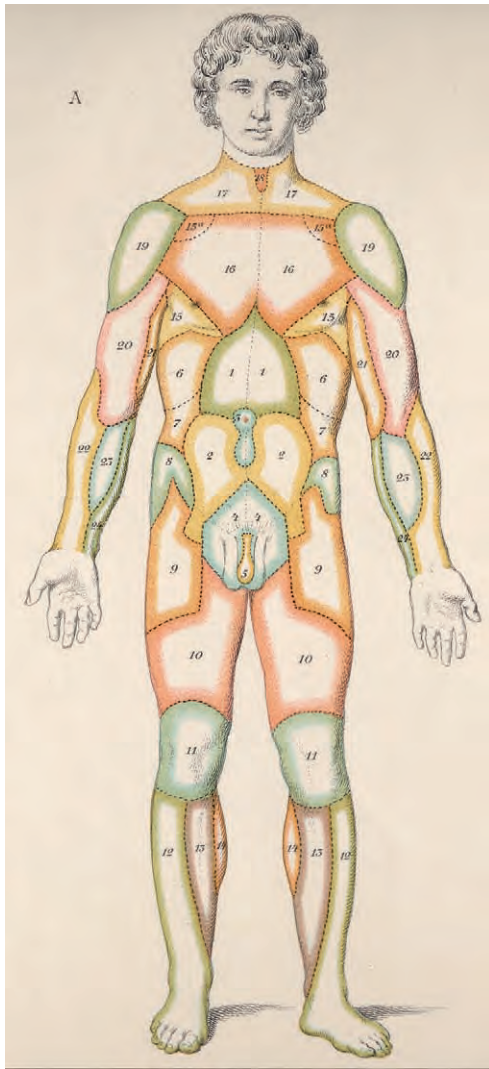


Fig. 2.23 The cutaneous vascular territories nourished by a single vessel. (Reproduced from Manchot C. *Die Hautarterien des menschlichen Körpers*. Leipzig: Vogel; 1889.)



Fig. 2.25 Jacques Joseph (1865–1934), carving a piece of ivory, before inserting it into the nasal dorsum. (Reproduced from Joseph J. *Nasenplastik und sonstige Gesichtsplastik nebst einem Anhang über Mammoplastik*. Leipzig: Kabitzsch; 1931.)

In 1887, John Orlando Roe (1848–1915), an otolaryngologist from Rochester, showed members of the New York Medical Society that reduction of a bulbous or “pug nose,” as he named it, under local anesthesia and on outpatient basis, was feasible.⁶² Four years later, he presented hump removal using scissors at the same society.⁶³ The following year, Robert Weir (1838–1927), a general surgeon from New York, described alar base excision, now eponymously named “Weir operation”, to lower an overprojected nose.⁶⁴

On the other side of the ocean, in Europe, aesthetic rhinoplasty started in Berlin, in about the same period, with Jacques Joseph (1865–1934), who codified the steps of the technique in a rigorous sequence, still used today after almost 100 years, with minimal variations (Fig. 2.25). For at least 20 years,

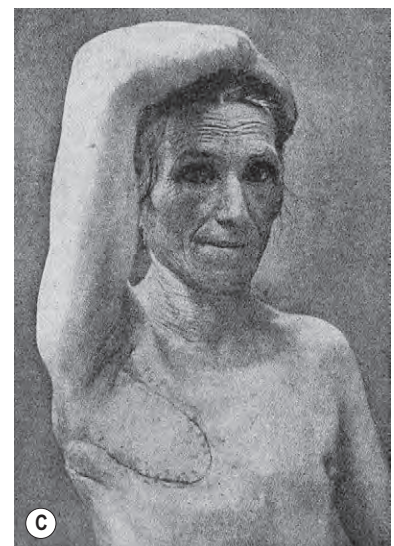
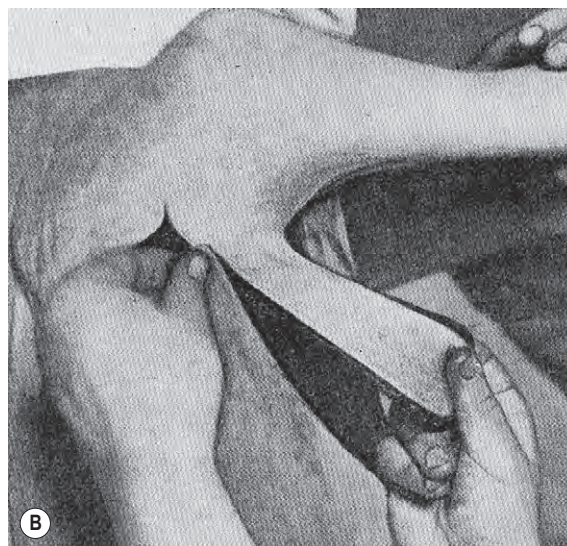
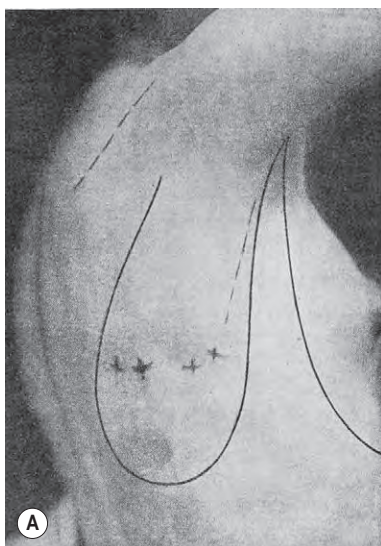


Fig. 2.24 The latissimus dorsi musculocutaneous flap according to Tansini. (A) Flap outlined. (B) Flap transposition. (C) Final result. (Reproduced from Tansini I. *Sopra il mio nuovo processo di amputazione della mammella*. Gazz Med It 1906;57:141.)

Joseph managed the aesthetic rhinoplasty scenario in Europe, receiving the most famous patients from every part of the world. His experience was included in a monumental work, *Nasenplastik und sonstige Gesichtsplastik (Rhinoplasty and other Facialplasties)*, published in 1931, which remained an unsurpassed text for several decades.⁶⁵

The development

The problem of the beauty doctors

The real explosion of aesthetic surgery took place in Europe and in the US between the two world wars.

The importance given to personal appearance produced, in the early 20th century and especially during the interwar period, a horde of quacks, charlatans, and beauty doctors often working in beauty salons, exclusively on a commercial basis. They advertised in newspapers, women's magazines, and yellow pages as cosmetic surgeons. They appealed to popular naivety by promising a more attractive look with simple, fast procedures on an outpatient basis, at relatively high cost and by insisting on how beautiful faces and noses were crucial in creating a favorable first impression for finding a job, or expanding social relationships.⁶⁶

To establish a barrier against beauty doctors and in an attempt to isolate them, true plastic surgeons, practicing reconstructive as well as aesthetic procedures, founded plastic surgical societies (see above). However, it was not an easy task because the general public was more interested in the achievements of cosmetic surgery than in the outcome of reconstructive procedures.

An example is given by Charles C. Miller (1880–1950), regarded as an “unscrupulous charlatan” by some or “the father of modern cosmetic surgery” by others for having published in 1907 *The Correction of Featural Imperfections*, a pioneering work on aesthetic procedures, where facial operations, such as double-chin excision, eyelid and nasolabial fold modification, were illustrated.⁶⁷ Miller made extensive use of paraffin injections, considered the ideal filler for improving saddle nose and cutaneous depressions. When paraffin was abandoned because of devastating local and systemic sequelae (paraffinomas, pulmonary embolism, phlebitis), he replaced it with crude rubber mixed with gutta-percha and ground in a mill.⁶⁸

Another borderline cosmetic surgeon was Henry J. Schireson (1881–1949), who knew a moment of fame in the US for having successfully operated on a British actress. Apart from this episode, he faced a series of lawsuits for malpractice which culminated in having his license revoked for a period of time. In 1944, *Time* defined him as the “king of quacks”.

Trained surgeons made considerable efforts to establish a positive view of plastic surgery. Their talent contributed to the transformation of a field regarded with suspicion into an accepted branch of surgery. Eastman Sheehan (1885–1951), Jacques Maliniak (1889–1976), Jerome P. Webster (1888–1974), Vilray Blair (1871–1955), Ferris Smith (1884–1957), and others all played important roles in creating plastic surgery's professional and public image during the years the specialty was taking shape. Sheehan, course director at Lemaître's International Clinic in Paris (Fig. 2.20), was elected President of the American Association of Plastic Surgeons in 1935, despite the controversial view of him by many American colleagues, who



Fig. 2.26 Result of a facelift carried out by Suzanne Noël (1878–1954) about 1925. (Reproduced from Noël S. *La Chirurgie Esthétique. Son rôle Sociale*. Paris: Masson, 1926.)

regarded Sheehan as a publicity-seeking skilled operator. Maliniak is best remembered as the founding member of the American Society of Plastic Surgeons in 1931. He was a prolific writer; *Sculpture in the Living* (1934)⁶⁹ and *Rhinoplasty and Restoration of Facial Contour* (1947)⁷⁰ are some examples. He had an important aesthetic surgical practice in New York, mainly for nose and breast. Webster was one of the founding fathers of US plastic surgery and a talented surgeon in the reconstructive as well as aesthetic fields. Smith, like Sheehan, was course director at Lemaître's International Clinic in Paris, and author of *Reconstructive Surgery of the Head and Neck*, issued in 1928 with a section devoted to aesthetic rhinoplasty.⁷¹

In Paris, Suzanne Noël (1878–1954), active feminist and founder of the Soroptimist Club of Europe, established a successful solo practice in the very exclusive 16th *arrondissement*. Her operations were simple but effective, mainly related to facial rejuvenation and entirely performed on an outpatient basis (Fig. 2.26). Major surgery, such as abdominoplasty or mammoplasty, was executed in a private clinic. In 1926, she published *La Chirurgie Esthétique. Son Rôle Sociale*, one of the first textbooks on this topic and the first written by a woman.⁷² In 1928 she was awarded the Legion of Honour. Raymond Passot (1886–1933), a leading Parisian aesthetic surgeon, added innovative techniques for breast ptosis, abdomen and facial rejuvenation. His book *La Chirurgie Esthétique Pure*, dating from 1931, showed a wide range of operations in the field of aesthetic surgery⁷³ (Fig. 2.27). Julien Bourguet (1876–1952), another Parisian cosmetic surgeon, became renowned for having first presented the transconjunctival approach for baggy eyelid correction in 1929.⁷⁴

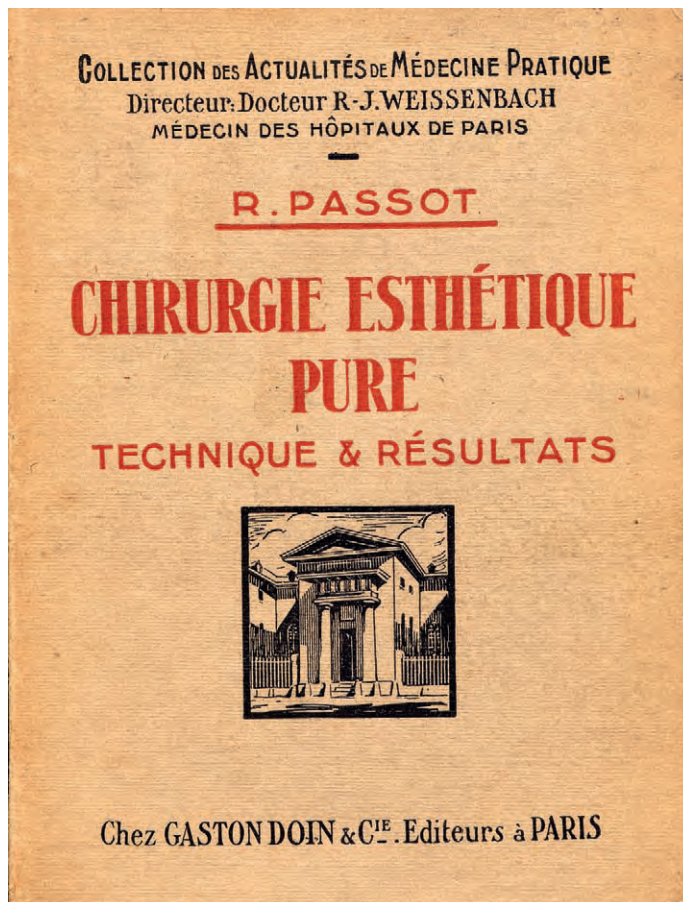


Fig. 2.27 The cover of the book on aesthetic surgery by Raymond Passot (1886–1933), published in 1931.

In Berlin, Jacques Joseph carried out a wide variety of cosmetic operations from rhinoplasty to reduction of prominent ears, facelifting and reduction mammoplasty.⁶⁵ Eugen Holländer (1867–1932) is credited with being the first one who reported on a facelifting. “Victim myself of the art of feminine persuasion, a few years ago, I performed the excision of a piece of skin along the hairline and the natural folds of the ageing wrinkles and I rejuvenated the drooping cheek for the satisfaction of the beholder”.⁷⁵ In a later publication he affirmed that this occurred in 1901 and that the patient was a Polish aristocrat.

In the same paper, Holländer showed two cases of facial atrophy treated by him with fat injection, and this was the first account reported in the literature.

Postwar aesthetic surgery

After World War II and in more recent years, aesthetic surgery grew significantly. The number of plastic surgeons around the world increased and the specialty expanded. Techniques for the correction of noses, faces, necks, eyelids, ears, chins, breasts, and abdomens improved considerably. New operations for solving a myriad of cosmetic problems developed. A typical example is management of the hypoplastic breast. Over the years it was treated with paraffin, sponge implants, fat grafts, and liquid silicone, with poor or unpleasant results. In the mid-1960s the silicone mammary prosthesis appeared on the market, representing the first convincing solution. Liposuction, introduced in the mid-1980s, soon became one of the most popular procedures. Faceliftings, fillers, botulinum toxin, and fat injection favorably improved the demand for facial rejuvenation.



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Psychological aspects of cosmetic surgical and minimally invasive treatments

David B. Sarwer and Mark B. Constantian

Disclosures: Dr. Sarwer has consulting relationships with Kythera, Medtronic, and Neothetics.

SYNOPSIS

- The last two decades have witnessed a dramatic increase in the number of persons who undergo cosmetic surgery and minimally invasive medical treatments designed to improve their appearance.
- Plastic surgeons have long been interested in the psychological factors that motivate individuals to undergo these procedures as well as the psychological changes that they frequently observe postoperatively.
- Early reports in this literature characterized most persons interested in changing their appearance with cosmetic surgery as suffering from a range of psychopathological conditions.
- More recent investigations of patients have focused on psychopathology but also other motivations.
- Body image dissatisfaction is commonly believed to be one of the strongest motivations for surgery. For some patients, however, this dissatisfaction may be severe and suggestive of the presence of body dysmorphic disorder or other forms of psychopathology with a body image component. Thus, these conditions are likely of greatest relevance to plastic surgeons.

The popularity of cosmetic surgical and minimally invasive treatments

According to the American Society of Plastic Surgeons, 15.6 million cosmetic surgical and minimally invasive treatments were performed in 2014.¹ The vast majority, nearly 14 million, were minimally invasive procedures such as Botox® injections and soft tissue fillers. Over 1.6 million were the traditional cosmetic surgical procedures such as breast augmentation and rhinoplasty. The total number of procedures has increased by 111% since 2000.¹ While these numbers certainly reflect the popularity of cosmetic procedures, they likely underestimate the true number of procedures performed annually in the United States, as physicians from specialties other than plastic surgery now offer many of these treatments.

There are a number of potential explanations for the growth in popularity in cosmetic surgery and minimally invasive treatments.^{2,3} Many treatments are safer and have shorter recovery periods than before. The shorter recovery period, as well as the much lower cost of minimally invasive treatments, have facilitated their rapid growth over the decade. Cosmetic procedures readily lend themselves to direct-to-consumer advertisements. In most major metropolitan areas, advertisements for these procedures are frequently seen on billboards and in local magazines. This marketing likely has contributed to the growth. The larger mass media and entertainment industries likely have contributed as well. Cosmetic surgery has long been a very popular topic for women's (and men's) fashion and beauty magazines, where articles often describe the latest advances in the field. The past decade also witnessed unprecedented coverage of cosmetic surgery on television, both in traditional media coverage and as the focus of reality-based television programs.⁵ At the same time, a growing number of celebrities publicly revealed their experiences with cosmetic surgery, a phenomenon not seen in Hollywood decades ago. These more overt influences play against a backdrop of relentless images of physical perfection depicted in magazines, television programs, movies, and the internet. The end result is that consumers can't help but be exposed to depictions of beauty as well as the message that cosmetic medical treatments are part of the path to physical perfection.

There are other potential explanations for the growth of cosmetic surgery as well. Evolutionary theories of physical attractiveness – which suggest that physical characteristics that demonstrate reproductive potential are the ones that are often seen as being most physically attractive – may play a role. Many facial procedures are undertaken to help an individual look more youthful and/or enhance their facial symmetry, key markers of physical attractiveness. Liposuction and abdominoplasty can decrease an individual's waist-to-hip ratio, which is another demonstrated marker of reproductive potential and “signal” of physical attractiveness.

Social psychological research on the role of physical appearance in daily life also can be used to understand the growth of cosmetic surgery as well as other appearance-enhancing behaviors. This research repeatedly has found that individuals who are more physically attractive are judged to have a number of more positive personality traits and receive preferential treatment in a range of social situations across the lifespan.⁶ With this in mind, interest in cosmetic surgery and minimally invasive treatments share similarities with other self-enhancement strategies, such as eating a healthy diet and exercising regularly.⁷

Psychosocial characteristics of patients interested in cosmetic surgery and minimally invasive treatments

Over the last 60 years, a large body of research on the psychological aspects of cosmetic surgery and minimally invasive treatments has developed.⁸ Many studies have investigated the psychological characteristics of patients who pursue these procedures; others have looked at the relationship of these characteristics to treatment outcomes. The first studies of this issue, conducted by plastic surgeons in collaboration with psychiatrists (many of whom appeared to be working from a psychodynamic theoretical orientation) involved clinical interviews of patients prior to their procedures. Perhaps not surprisingly, these studies described large numbers of patients as suffering from significant psychopathology.^{9,10} Large numbers of individuals were characterized as suffering from depression, personality disorders (typically narcissistic personality disorder) and even schizophrenia. Many of these early reports also contain elaborate interpretations of the role of unconscious conflicts and poor parental relationships in the decision to seek surgery. There is no evidence, however, to suggest that such interpretations are necessarily valid or useful in determining patients' appropriateness for surgery.^{11,12} As could be anticipated, those patients suffering with these issues were thought to be likely to experience poor postoperative psychological outcomes.

Studies conducted since the 1980s typically have included the use of psychometric measures of personality characteristics rather than or in addition to clinical interviews of prospective patients. These studies, as compared to the previous investigations, typically have found less psychopathology.¹³⁻¹⁶ Nevertheless, both sets of studies suffer from methodological problems that have made interpretation of these conflicting findings difficult.^{11,12,17} Thus, the rate of psychopathology among cosmetic surgery patients remains poorly understood. Perhaps more importantly, the relationship between preoperative psychopathology and postoperative outcomes, with few exceptions, is largely unknown.

Much of the more contemporary research on the psychosocial characteristics of cosmetic surgery patients has focused on two issues. The first is the motivations of persons who present for these procedures; body image dissatisfaction is believed to be central to these motivations. The second is the occurrence of formal psychopathology and whether the presence of significant psychiatric illness contraindicates treatment.

Body image dissatisfaction as a motivation for cosmetic medical treatment

Patients present for cosmetic medical treatments with a variety of motivations. These motivations have been described as internal (e.g., desire to improve one's self-esteem) or external (e.g., undergoing surgery in order to find a romantic partner).¹⁸ Although patients may struggle to verbalize their specific motivations for surgery to others (including friends, family members, and their treating physician), those with internal motivations are thought to be more likely to have their postoperative expectations met.¹⁹

Body image dissatisfaction is believed to be the most common motivation for a cosmetic procedure. The last several decades have witnessed a growing interest in the psychological construct of body image.²⁰ Body image has been defined in several ways. A commonly used definition suggests that body image consists of perceptions, thoughts, and feelings associated with the body and bodily experience. While this definition describes the multidimensional nature of the construct, it does not highlight body image behaviors, such as motivations for changing one's appearance through cosmetic procedures. Cash and Smolak have described body image as "the psychological experience of embodiment".²¹ This description conveys a sense of importance of the role of body image in larger psychological constructs like quality of life.

Body image is believed to contribute to self-esteem and quality of life.^{22,23} Much of the early research on body image focused on the weight and shape concerns of individuals with eating disorders. As research into the global obesity problem matured in the 1990s, the body image concerns of overweight and obese individuals garnered more attention.²⁴ Body image concerns can be thought of as both global and specific. Body image dissatisfaction is often correlated with body weight.²² However, the strength of this relationship is not as strong as would be intuitively thought. This finding is consistent with theories of body image, which have suggested that there may be little relationship between what one thinks about the body and the objective reality of one's appearance.²¹

Independent of body weight, most individuals also report more concerns with specific features of their appearance. This is particularly true among individuals who presented for cosmetic procedures, who often report dissatisfaction focused on a given feature rather than a more global dissatisfaction with their entire body. Women are typically far more dissatisfied with their body image than men.²³ Differences also exist across ethnic groups. African-American women, as compared to Caucasian women, typically report less body image dissatisfaction. Among ethnic groups, body image dissatisfaction appears to be related to the degree of acculturation into more Westernized lifestyles.

Some degree of body image dissatisfaction appears to be "normative" in Western society and likely results from society's pervasive emphasis on thinness as the ideal body type. Body image dissatisfaction is believed to motivate a number of appearance-enhancing behaviors, including weight loss, physical activity, fashion and cosmetic purchases, and cosmetic procedures.²⁴ Body image dissatisfaction, and its role in the pursuit of cosmetic medical treatments, has been the focus

of much of the recent study of cosmetic surgery patients.²⁵⁻²⁷ Individuals who seek cosmetic procedures typically report heightened body image dissatisfaction preoperatively.^{7,28-31} For example, breast augmentation candidates report greater dissatisfaction with their breasts compared to other small-breasted women who do not seek breast augmentation.^{13,15} Similarly, individuals interested in rhinoplasty reported more appearance concerns as compared to those of age- and gender-matched controls presenting for non-appearance-altering surgery.³² Thus, some degree of body image dissatisfaction is believed to be a prerequisite to cosmetic surgery. At the same time, body image dissatisfaction, particularly extreme body image dissatisfaction that impacts daily functioning, is a symptom of a number of psychiatric disorders. These include eating disorders, social anxiety disorder, and gender dysphoria. While all psychiatric disorders are likely to be represented among the large population of persons presenting for cosmetic treatments, the psychiatric disorder with perhaps the greatest relevance to cosmetic medical treatment is body dysmorphic disorder. At the same time, eating disorders and depression also warrant particular attention.

Formal psychopathology among patients interested in cosmetic surgical and minimally invasive treatments

Body dysmorphic disorder

Body dysmorphic disorder (BDD) is characterized as a preoccupation with a slight or nonobservable defect in appearance that is associated with obsessive thinking and compulsive behaviors and which leads to a disruption in the activities of daily life.³³ Case reports of patients who likely had the disorder, described as “minimal deformity” or “insatiable” patients, appeared in the plastic surgery and dermatology literatures in the 1960s and 1970s.³⁴⁻³⁷ These case reports, appearing nearly two decades before BDD was formally recognized as a psychiatric disorder, detailed patients who requested multiple procedures to improve slight or imagined defects in appearance; most reported significant dissatisfaction with postoperative treatment as well.

Identifying and diagnosing BDD in cosmetic treatment settings can be challenging.^{38,39} According to DSM-5’s first diagnostic criterion for BDD, an individual must be preoccupied with one or more perceived defects in appearance which are either “slight” or nonobservable to others.³³ Most patients presenting for cosmetic treatments have “normal” features that that they wish to enhance; others may desire correction of slight imperfections. Thus, the majority of patients could meet this criterion.

The second diagnostic criterion describes engagement in repetitive, appearance-focused behaviors, such as comparing one’s appearance to that of other people or repeatedly checking one’s appearance in the mirror. Many cosmetic medical patients engage in these behaviors; others report that they have spent large amounts of time reviewing images of celebrities in order to find examples of how they wish specific features to look. It is not uncommon for individuals who seek cosmetic treatments to report self-consciousness in social situations or

in situations where their perceived “defect” may be more noticeable to others (e.g., a woman with concerns about her nose size may report self-consciousness when someone sits next to her at a restaurant). Still, others may avoid such situations or engage in camouflaging behaviors. These examples of concerns and behaviors, while indicative of body image dissatisfaction, likely do not meet the third criteria for BDD (experiencing clinically significant distress or impairment in social, occupational, or other important areas of functioning). However, a patient who is reporting symptoms of anxiety and depression because of her nose, or who is socially isolated or unable to work because of her appearance concerns, likely would meet diagnostic criteria. Thus, in cosmetic settings, the degree of distress and impairment in functioning experienced by the patient likely differentiates a cosmetic surgery patient with “normative” body image dissatisfaction from one who is in fact suffering from BDD.^{38,39}

Rates of BDD among cosmetic treatment populations

A number of studies have investigated the rate of BDD among individuals presenting for cosmetic surgery.⁴⁰ Among American samples, rates of 7–13% have been reported.^{7,41,42} International studies have reported rates ranging from 2.9%–53%.⁴³⁻⁵¹ Studies with the highest rates of BDD have typically used unspecified clinical interviews to establish the diagnoses. Thus, there are concerns about the validity of these results. International studies which have used more rigorous methods have found rates ranging from 3.2 to 16%.

Seven studies have investigated the rate of BDD among patients seeking rhinoplasty and reported rates ranging from 12–33%.⁵²⁻⁵⁶ The higher rates reported among rhinoplasty patients is not surprising given that the nose is one of the most common areas of concern among persons with BDD.⁵⁷ Among 13 patients seeking Botox® injections for perceived hyperhidrosis, 23% met criteria for BDD.⁵⁸ In a study of 137 patients in Australia, 2.9% met criteria for BDD.⁴³ Investigators have also turned their attention to evaluating BDD among patients seeking less common procedures, including requests for genital cosmetic surgery. Veale and colleagues found that 18% of women seeking labiaplasty met criteria for the diagnosis.^{59,60}

BDD is similarly common among persons who seek dermatological treatment, with rates typically ranging from 4.2–15%.^{50,61-68} Acne patients treated with isotretinoin (Accutane) have been found to be twice as likely to meet criteria for BDD,⁶⁶ a finding that is of interest given the association between suicidality and use of this treatment as well as the high rates of suicidal ideation and attempts reported among those with BDD.⁶⁹

BDD also has been studied among persons seeking reconstructive procedures. Three studies have examined the rate of BDD among persons seeking reconstructive surgical procedures, such as scar revision and breast reconstruction, with 2–16% of patients reporting distress or concern with their appearance consistent with BDD.^{41,42,70} A recent study examined BDD symptoms among 188 women undergoing breast reconstruction secondary to mastectomy; 17% met criteria for BDD, and women undergoing delayed reconstruction (versus immediate) were more likely to meet criteria.⁷¹ Although women with actual breast deformities due to mastectomy

would likely not meet full criteria for BDD, individuals with objective defects can become preoccupied with their appearance and experience significant distress and functional impairment.

Use of cosmetic medical treatments among individuals with BDD

A number of studies have investigated the history of cosmetic procedures among persons with an established diagnosis of BDD.⁷²⁻⁷⁴ In one of the earliest studies, 48% of individuals with BDD reported having sought cosmetic or dermatological treatment, with 26% having undergone one or more cosmetic procedures.⁷⁴ Two larger studies have suggested that over 70% of patients had sought and more than 64% had received a cosmetic treatment.^{72,73} These reports are not particularly surprising. Individuals with BDD believe, often with delusional intensity, that their appearance is truly flawed. Many believe that the only way to reduce their appearance-related distress is to actually change their appearance via cosmetic medical treatment. In fact, individuals with BDD are nearly as likely to pursue treatments from dermatologists, paraprofessionals, and plastic surgeons as they are from psychologists or psychiatrists.⁷⁵

While many individuals with BDD are able to obtain cosmetic treatments, a sizable percentage report that they were unable to receive a desired treatment. Surveys suggest that 80% of plastic surgeons and 62% of dermatologic surgeons have refused to perform cosmetic procedures on individuals believed to have BDD.^{76,77} Unfortunately, in today's competitive cosmetic procedure market, patients with BDD who are denied treatments by one provider can engage in "doctor shopping" until they find a provider willing to perform their desired procedure.

In some instances, patients with BDD can become so distressed about their perceived appearance defects that they take matters into their own hands and perform "do-it-yourself" procedures.^{78,79}

Cosmetic treatment outcomes among persons with BDD

Individuals with BDD are often convinced that cosmetic treatments will alleviate their appearance-related preoccupation and distress. However, evidence suggests that cosmetic treatments rarely improve BDD and patients are frequently dissatisfied with treatment outcomes.^{72,74,78,79} For example, a study of 200 persons with BDD found that only 3.6% of 528 procedures resulted in improvement in overall BDD symptoms.⁷²

Few studies have prospectively examined cosmetic treatment outcome among individuals with BDD. Tignol and colleagues⁸⁰ evaluated 24 cosmetic surgery patients who sought treatment for minimal appearance defects; 10 of these patients had been diagnosed with BDD preoperatively. Five years later, seven of the ten patients had undergone cosmetic surgery. Among these seven, remission was reported by only one, while the other six continued to meet diagnostic criteria for BDD. New areas of concern developed in five patients. A prospective study of 166 individuals who sought rhinoplasty found that greater preoperative BDD symptoms predicted dissatisfaction with treatment postoperatively.⁸¹ Similarly, a

study of 127 women who had undergone cosmetic treatment reported that women with higher levels of BDD symptoms were more likely to be dissatisfied with their treatment outcome and were more likely to have ever been rejected for cosmetic treatments compared to those with low BDD symptom levels.⁸² Phillips *et al.* conducted a prospective, naturalistic study of 161 individuals diagnosed with BDD and found that receipt of cosmetic treatment did not predict remission from BDD one year later.⁸³ Overall, these findings are consistent with retrospective reports regarding the likelihood of poor outcomes following cosmetic treatments among persons with BDD.

In contrast, two recent studies have suggested that some individuals with BDD may benefit from cosmetic treatments. A prospective study of 31 patients with mild to moderate BDD who sought and received rhinoplasty found that, postoperatively, 81% had a complete remission of BDD symptoms; 90% were satisfied with their postoperative outcome.⁸⁴ However, this study had some significant limitations, such as the small sample and inclusion of patients who were rated as having "marked nasal deformity" (calling into question whether they would meet diagnostic criteria for BDD). Thus, the conclusion that rhinoplasty benefits patients with mild to moderate BDD is likely unfounded.⁸⁵ Another recent prospective study of women seeking labiaplasty ($n = 49$), nine of whom met criteria for BDD via self-report and clinical interview preoperatively, found that eight experienced a remission from BDD symptoms at a 3-month postoperative assessment,⁶⁰ and four reported longer-term remission from BDD. Interestingly, the one woman who still met criteria for BDD postoperatively did so because of a different appearance preoccupation (nose) but reported satisfaction with her labiaplasty.

In addition to the risks for poor outcomes and dissatisfaction with treatment, patients with BDD are known to have high risks for suicide. The mean annual suicide attempt rate for persons with BDD is 2.6%, while the mean suicidal ideation rate is 57.8%.⁶⁹ Unmet cosmetic treatment expectations could fuel suicidal ideation and/or suicide attempts in some patients with BDD. Treating physicians also face risks when knowingly or unknowingly performing cosmetic procedures on patients with BDD. At a minimum, patients with BDD may present as being "difficult" or hard to manage for providers and their staff.^{86,87} Providers may also face legal risks, as patients with BDD have threatened or pursued legal action against their treating physicians.^{42,76,77} Surveys of cosmetic treatment providers suggest that between 9% and 29% of physicians have been threatened legally by a patient with BDD.^{76,77} Two percent of cosmetic and dermatological surgeons report being threatened with physical harm by patients with BDD. Tragically, some providers have been murdered by patients with or suspected of having BDD.⁸⁸

Due to the safety risks for both patients and providers along with the evidence that cosmetic treatment outcomes among persons with BDD are typically poor, BDD appears to be a contraindication for cosmetic treatments. Given that persons with BDD frequently seek cosmetic treatments, screening for BDD is recommended in cosmetic treatment settings.

Clinical presentation of patients with BDD

A number of still-unanswered questions emerge from the body image and body dysmorphic disorder literature: (1)

What drives patients with normal features or minimal deformities to undergo repeated plastic surgeries on one or more body areas? (2) Why is there often such poor correlation between the degree of preoperative deformity and the drive to surgery that it provokes? (3) Why are patients who have undergone multiple cosmetic surgeries so likely to be unhappy with their surgical results, even when they appear to be successful? (4) If body dysmorphic disorder is driven by the media and the obsession of popular culture with beauty and being thin, why are some reconstructive patients just as difficult to please?⁸⁸ (5) Why do some postoperative patients become so irrationally angry that they are beyond reason? (6) Finally, why do many of these unhappy patients have turbulent family relationships?

Twenty years ago, one of us (MBC) saw three patients in relatively quick succession who all had tumultuous postoperative courses after reconstructive nasal surgery – doubly ironic because each patient had an entirely successful surgical outcome. One was a university professor who resigned her position to become a recluse because she believed that her reconstructed nose now pointed toward the ceiling. She remained inconsolable by logic or photographic analysis. When I advised against further surgery, she wrote a letter that concluded, “I feel so terribly betrayed... You have robbed me of my family, my friends, and my joy in living.” The second patient was a physician’s wife who hid in her bedroom for months after surgery, unable to function or care for her family because of perceived but invisible nasal deformities. The third patient abandoned his business, abused alcohol heavily, and unsuccessfully tried to amputate his reconstructed nose.⁷⁸ All of these patients seemed like excellent surgical candidates preoperatively but revealed themselves to meet the diagnostic criteria for BDD after surgery. Postoperatively, they could not be reassured: all were convinced that their results were failures and that they needed additional surgery.

Soon thereafter, a young man came for secondary rhinoplasty who said, “I had body dysmorphic disorder but I have recovered.” With the approval of his therapist, one of us (MBC) performed his revision rhinoplasty. His postoperative course was smooth. Later, the surgeon requested a letter describing his body dysmorphic disorder experience, since most surgeons had never treated patients who recovered. His four-page, single-spaced autobiography chronicled an intense, traumatic childhood, the desertion of his father, an abusive stepfather who relentlessly ridiculed the child’s nose, family alienation, his brother’s suicide, drug abuse, and his mother’s abandonment. This observation led to further speculation on the relationship between BDD and childhood abuse or neglect, which was subsequently reported in the literature.⁸⁹

This hypothesis led to a report of 20 secondary rhinoplasty patients with similar personal and family characteristics who had undergone a total of 134 rhinoplasties, almost 7 each.⁹⁰ All had undergone multiple rhinoplasties and other cosmetic operations; they were perfectionistic, demanding, and depressed; and 80% of their original unoperated noses had been straight and symmetrical. When asked, “Why did you have surgery?” they gave answers like these: “Because my nose wasn’t perfect enough”; “Because my mother wanted me to be as beautiful as she was”; “Because my mother told me, ‘You were the ugliest baby I ever saw’”; and perhaps the saddest one, “I had surgery so people would love me.”

These observations led to further study of the psychosocial history of 100 secondary rhinoplasty patients.^{91,92} Half of the patients originally had noses with dorsal humps (the most common motivation for rhinoplasty), and half originally had straight noses. Twenty-nine had straight, functional noses that the patients knew were normal; yet they had surgery anyway. The data suggested that the smaller the deformity, the greater the likelihood of depression, history of childhood trauma, and the lower the patients’ satisfaction with the surgical results. Secondary rhinoplasty patients who originally had straight noses had undergone three times as many rhinoplasties and had three times the trauma prevalence of patients who originally had dorsal humps. Among 29 patients who were depressed, had undergone more than three cosmetic operations of any type, and whose motivation for the first rhinoplasty had been to “perfect” a subjectively normal nose (which defines body dysmorphic disorder), the prevalence of childhood trauma was an astonishing 93%. The surgical satisfaction rate after one operation was only 3%. Subsequent studies have indicated that many revision rhinoplasty patients also screen positive for post-traumatic stress disorder, especially if they had childhood trauma histories, and that successful reconstructive surgery can decrease their avoidance and re-experiencing symptoms.⁹³ Mediation analysis indicated that a history of childhood abuse or neglect was the most significant factor connecting patient satisfaction and the number of previous surgeries; in other words, childhood trauma patients had undergone the most cosmetic surgeries and were the most likely to be unhappy with the results of additional procedures.⁹¹ Random forest analysis indicated that the number of prior surgeries was the most significant predictor of surgical success for patients who originally had dorsal humps, but that childhood trauma was the most significant factor predicting success for patients who originally had straight, normal noses.⁹²

Childhood trauma is implicated in many types of diseases, including chronic pain syndromes, fibromyalgia, cardiovascular and pulmonary disease, cancer, asthma, morbid obesity, mental health disorders, and autoimmune disease, which accounts in part for the reported incidence of body dysmorphic disorder even in reconstructive patients.^{70,71,88,94,95–99} Of particular interest and relevance to plastic surgeons is the connection between childhood trauma, eating disorders, and body image. A number of studies have shown a strong correlation between body image and childhood trauma, particularly sexual abuse, depression, eating disorders, and obesity.^{97,99–101}

What evidence is there that BDD patients display signs of neglect or abuse? One study indicated that 78.7% of 75 patients with confirmed BDD had histories of neglect or abuse.⁸⁹ Other reports document associated traits: poor social functioning, social anxiety, depression, anxiety, anger, and somatic symptoms, neuroticism, eating disorders, post-traumatic stress disorder, and obsessive compulsive disorder.^{102–112}

To date, efforts to identify abnormalities in neuroanatomy, neurotransmitters, or genetic expression or allelic variation have not yielded consistent information about the pathogenesis of body dysmorphic disorder. However, fMRIs of body dysmorphic patients have documented overactivity in the thalamus and amygdala and a left-to-right volume asymmetry in the caudate nucleus, changes that are coincidentally consistent with findings in patients with histories of childhood

trauma and post-traumatic stress disorder.¹⁰⁸ Adding even further complexity is recognition that family environment influences genetic factors, which in turn work together to create both personality and psychopathology. Although only a small number of genes have been studied to date, both genome-wide association studies and epigenetic research have documented variations in the hypophyseal–pituitary axis and dopamine and serotonin transmission that may affect susceptibility to trauma or, conversely, produce resilience.¹⁰⁹

What are the clinical implications of these relationships? Most plastic surgeons do not routinely take trauma histories or inquire about their patients' childhoods, and not every person subjected to abuse or neglect is susceptible to their damaging effects. Yet all patients have life histories. Abuse by caregivers may be disempowering or falsely empowering, distorting or destroying the traits that functional adults must possess: self-esteem, "boundaries" (self-protection and containment against offending others), a sense of reality, and the ability to live moderately and independently. Abused and neglected patients live at the extremes, depending on the types of trauma they have experienced. For example, disempowered patients lack self-esteem, cannot articulate surgical goals, forget appointments, and may manifest victim behavior; falsely empowered patients become grandiose, demand extra attention, may dictate the operative plan, and expect perfection (Table 3.1). Only when surgeons consider their patients' pasts will their current behaviors become understandable as remnants of adapted responses to abuse or neglect.¹¹⁰

The shadow factor of childhood abuse and neglect, so regrettably common in our culture, may, in part, explain why the severity of our patients' deformities does not always correspond to the drive for surgery that it provokes, why so many of their lives and family relationships are chaotic, and why it is so hard to reason with some unhappy patients. The trauma link complements what is currently known about body dysmorphic disorder and may be one of the keys to understanding some of our unhappiest plastic surgery patients.

Depression

The potential presence of major depression or other mood disorders also warrants particular attention by the physician offering cosmetic treatments. At least one study has suggested that approximately 20% of persons presenting for cosmetic surgery are engaged in mental health treatment, most typically the use of an antidepressant or other psychiatric medication.¹¹¹ Women considering breast augmentation or those with breast implants have been found to report a higher rate of outpatient psychotherapy,¹⁵ psychopharmacologic treatments,¹¹¹ and psychiatric hospitalizations,¹¹² as compared to other cosmetic surgery patients or women from the general population. Although these studies suggest that the rate of psychopathology may be higher among patients with breast implants, the investigations provided no information on the specific psychiatric diagnoses of these women.

Table 3.1 Characteristic behaviors of disempowered and falsely empowered patients

Disempowered patients	Falsely empowered patients
No self-esteem Unjustifiably untrusting or fearful Unable to make decisions Unsure of themselves or surgeon Require extra time of surgeon and staff Manifest victim behavior	Grandiosity False sense of superiority Try to dictate operative plan Expect to be seen on holidays or weekends Demand extra time of surgeon and staff Request special fees and/or discounts
Overly sensitive to surgical advice Take everything as criticism No sense of humor May exercise covert manipulations	Argue Interrupt May act offensively or manipulatively and try to control the surgical process
Unable to articulate surgical goals Seem inarticulate, disconnected, non-relational Have exaggerated or imperceptible deformities May have controlling parents or spouse	Unrealistically precise about surgical goals Expect perfection Have exaggerated or imperceptible deformities Argumentative with staff
Possible histories of alcohol abuse and/or antidepressant use Depression, migraines, fibromyalgia Eating disorders or obsessive compulsive behavior History of multiple surgeries without adequately considering risks	Possible histories of stimulant use, risk-taking, gambling, high-risk sports or professions Work or sex addictions High-intensity lives History of multiple surgeries without adequately considering risks
Unable to perform simple postsurgical care Forget appointments, unable to make decisions Do not remember or follow written instructions Request and need constant advice and reassurance via phone or email May self-injure, become reclusive or threaten suicide	Disregard perioperative instructions Demand extra, holiday, or weekend appointments Arbitrarily alter perioperative instructions Act entitled Guarded; remote; may reject routine postoperative care May become aggressive or threatening
May have body shame	May have body shame

Over the past 15 years, seven epidemiological studies investigating the relationship between silicone gel-filled breast implants and all-cause mortality have found an association between breast augmentation and suicide.¹¹³ These studies, which focused on women who received these implants for cosmetic purposes, suggest that the rate of suicide is two to three times higher than rates in other cosmetic surgery patients or estimated rates in the general population. (Women who received breast implants as part of breast reconstruction were not studied.) Potential explanations of the relationship between breast implants and suicide primarily have focused on the preoperative psychosocial status and functioning of the women.^{25,113,114} Women who undergo cosmetic breast augmentation have been shown to have a number of distinguishing demographic characteristics. They are more likely to report more lifetime sexual partners and a greater use of oral contraceptives, be younger at the time of their first pregnancy, and have a history of terminated pregnancies.^{115,116} They also have been found to be more frequent users of alcohol and tobacco.^{14,116,117} Many of these characteristics are markers of psychopathology, in and of themselves, risk factors for suicide.

Only one of the seven epidemiological studies provided any information on the psychiatric history of the women studied. This study found a higher rate of previous psychiatric hospitalizations among women with breast implants in comparison to both women who received other cosmetic procedures and women who underwent breast reduction.¹¹² A history of psychiatric hospitalizations is one of the strongest predictors of suicide among women in the general population.¹¹⁸ Unfortunately, Jacobsen and colleagues did not report information on diagnosis, history of illness, or other psychiatric treatments for the women in their sample.¹¹² Thus, more specific information on the relationship is not available. Though these studies have documented that there is a relationship between breast augmentation and suicide, it is important to note that breast implants or breast augmentation surgery does not cause suicide. Rather, it appears that the individual personality characteristics and experiences more likely contribute to the relationship.

Eating disorders

Given the excessive body image dissatisfaction reported by patients with eating disorder, these disorders may occur with some frequency among those who seek cosmetic surgery. Persons with eating disorders may erroneously believe that cosmetic treatments will improve their immense dissatisfaction with their bodies. Eating disorders may be a particular concern for women (and men) who seek body contouring procedures, including liposuction, abdominoplasty, as well as breast augmentation. These patients may mistakenly believe that these procedures can reshape their bodies in a way that restrictive eating and/or maladaptive compensatory behaviors cannot. Women who present for cosmetic breast augmentation are frequently below average weight^{13,15,31} and report greater exercise compared to physically similar women not seeking breast augmentation,¹³ both of which also may be suggestive of eating psychopathology.

In summary, the psychological functioning of cosmetic surgery patients has been of interest to both the physicians who offer these treatments, as well as mental health professionals, for decades. This interest predates the prolific growth

of aesthetic medical treatments seen in the past two decades. With the wide range of patients who seek cosmetic surgery, all psychiatric diagnoses are likely to be found. Most salient to cosmetic surgery are likely psychiatric conditions with a body image component – body dysmorphic disorder and eating disorders as well as depression. Studies suggest that between 5% and 15% of patients seeking cosmetic surgery suffer from BDD, indicating that providers may encounter these patients in their practice on a regular basis. Although it makes intuitive sense that the weight and shape concerns seen in eating disorders may be related to interest and pursuit of cosmetic surgery, research investigating this relationship is lacking. The most concerning relationship between cosmetic surgery and psychopathology is the link between breast implants and suicide. This relationship clearly warrants further study.

Psychosocial status following cosmetic medical treatments

Numerous studies have suggested that 80–90% of patients report satisfaction with the results of their cosmetic medical treatments.^{16,119–122} Patients also have been found to report significant improvements in body image.^{16,121,123–125} Most studies have found these changes within the first two years of surgery, although one investigation has shown improvements in body image enduring for five years after surgery.^{126,127}

Studies of psychosocial functioning beyond body image have produced mixed results. For example, a number of relatively recent studies have looked at changes in self-esteem following cosmetic medical treatments. This is a particularly relevant construct, as these treatments are often marketed with the promise of improving self-esteem. Some studies have documented the improvements in self-esteem.^{127–129} Other studies have not found statistically significant improvements in self-esteem.^{130–133} However, this also may be a function of methodology. For example, if asked directly whether or not surgery improved self-esteem, women who underwent breast augmentation report improvements.^{129,130,133} In contrast, studies which have used psychometric measures of self-esteem have found equivocal results.^{119,121,134–136} At least one investigation has shown that while self-esteem may improve in the first few years after surgery,¹²⁸ these benefits appear to dissipate over time.

Studies that have investigated the relationship between cosmetic medical procedures and depression also have found mixed results. Some reports show an improvement in depressive symptoms.^{137–139} In contrast, other studies have found no appreciable changes in depressive symptoms after treatment.^{126,132,140}

Postoperative satisfaction and the psychological benefits associated with cosmetic surgery may be negatively impacted by the occurrence of a postoperative complication.¹⁹ At least one study found that breast augmentation patients who experienced postoperative complications reported less favorable changes in body image in the first two years following surgery.¹²⁴ Statistics from the American Society of Plastic Surgeons indicate that approximately 50% of patients return for a second procedure at some point in the future.¹ Unfortunately, it is unclear if these patients are returning for a second procedure because they are dissatisfied with the outcome of

the first procedure or if they were satisfied with the outcome and are now interested in modifying another aspect of their appearance.

Assessment of psychosocial functioning prior to cosmetic medical treatment

Physicians who perform cosmetic surgical and minimally invasive treatments should evaluate and monitor the psychosocial status and functioning of patients who seek these procedures. Most patients who present for these treatments are thought to be psychologically stable. Prospective patients typically have specific appearance concerns, internal motivations, and realistic postoperative expectations. Thus, most patients do not need a psychological evaluation prior to treatment. Nonetheless, a sizable minority of individuals who present for aesthetic medical procedures may present with a range of psychiatric conditions – BDD, depression, eating disorders – that may contraindicate a cosmetic procedure.

In the competitive marketplace of aesthetic medical treatment, where physicians from a range of medical specialties offer cosmetic procedures, it is unlikely that any physician currently requires new patients to undergo a mental health evaluation prior to treatment. Such a practice would likely drive patients to other practices almost instantaneously. More importantly, given the lack of reliable evidence suggesting a relationship between preoperative psychosocial status and postoperative outcomes (with perhaps the exception of BDD), recommendations for such routine evaluations is not warranted.²⁰ Rather, physicians who offer aesthetic procedures, like all medical professionals, should assess and screen for the presence of psychopathology as part of a medical history and completion of physical examination. Unfortunately, most physicians (or their delegates) likely skip this part of the assessment and, as a result, likely fail to identify patients who may exhibit symptoms of significant psychopathology or have a history of abuse or neglect that may impact their psychosocial functioning.

Specific questions asked during the initial consultation can be an effective way of identifying patients with mental health issues. These questions can help safeguard providers against patients who could become litigious or violent; it also provides an opportunity to direct patients to appropriate psychiatric treatment if needed. Patients should be informed that these questions are part of the practice's standard initial consultation procedures and are asked of all prospective patients. Such a statement can help reassure patients that they are not being "singled out" and may encourage an honest disclosure of information.

Psychiatric history and status

The assessment of the patients' psychiatric history and current status is a central part of the evaluation. Approximately 20% of patients who seek cosmetic surgery or minimally invasive procedures report using a psychiatric medication at the time of treatment.^{115,141} As mental health professionals frequently observe, patients who receive these medications from a primary care physician often do not experience complete relief from their symptoms. Thus, a psychopharmacologic

evaluation should be considered if symptoms do not appear to be well controlled. If a patient is in treatment with another mental health professional, the surgeon should contact this professional and, as appropriate, discuss the patient's appropriateness for treatment.

For patients with current symptoms of BDD or a history of psychiatric disorders or psychiatric hospitalization, a preoperative mental health evaluation is recommended before proceeding with surgery. If a patient discloses (s)he is currently receiving psychiatric or psychological treatment, the surgeon or staff should request permission to contact the patient's mental healthcare provider in order to discuss the appropriateness of surgery. Surgeons should be cautious about proceeding with surgery if the patient refuses to allow contact with their mental healthcare provider.

Motivations and expectations

The surgeon also should inquire about motivations and expectations for aesthetic treatment. In assessing motivations, the provider may want to ask, "When did you first think about changing your appearance?" Similarly, it may be instructive to ask, "What other things have you done to improve your appearance?" In addition to providing important clinical information, these questions also may reveal the presence of some obsessive or delusional thinking, as well as compulsive or bizarre behaviors, related to physical appearance. Some patients may report that they have tried several "do-it-yourself" treatments, such as non-FDA approved treatments, in an attempt to improve their appearance, many of which may be unhelpful and, in some cases, potentially dangerous.

Patients should be asked how romantic partners, family members, and close friends feel about the decision to change a physical feature. While these individuals likely influence patients' decision-making process, their role may not be as great as intuitively thought. For example, candidates for cosmetic breast augmentation surgery reported that their decision to seek surgery was influenced more by their own feelings about their appearance than it was influenced by the thoughts of their romantic partners. Nevertheless, patients who seek treatment specifically to please a current partner, or attract a new one, are thought to be less likely to be satisfied with their postoperative outcomes. Thus, the treatment provider should inquire about patients' general expectations about how the change in appearance, which may be rather subtle and potentially unnoticed by others, will influence their lives.

There is some evidence to suggest that individuals who undergo cosmetic procedures are seen as younger looking and more attractive. However, there is no evidence to suggest that aesthetic procedures directly impact interpersonal relationships. Therefore, patients should be reminded that it is impossible to predict how others will respond to their changed appearance. Some patients may find that few people notice the change in their appearance, while others may have the experience that everyone seems to notice them. While some patients may find this attention pleasurable, others may find it uncomfortable. To assess this issue, patients should be asked how they anticipate their lives will be different following treatment. The experience of unmet postoperative

expectations is another possible explanation of the relationship between cosmetic breast augmentation and suicide.¹²¹ Some women may present for breast augmentation surgery with unrealistic expectations about the effect that the procedure will have on their romantic relationships or daily functioning. When these expectations are not met, they may become despondent, depressed, and potentially suicidal.

Physical appearance and body image

Individuals presenting for an aesthetic treatment should be able to articulate specific concerns about their appearance that should be visible to the treatment provider with little effort. Patients who are markedly distressed about slight defects that are not readily visible may be suffering from BDD. The degree of emotional distress and impairment, rather than the specific nature of the defect, may be more accurate indicators of BDD in aesthetic medical patients.

Aesthetic medical treatment providers, and consulting mental health professionals, should be prepared to ask specific questions to assess for the presence of BDD. Individuals with nonexistent or minimal flaws who spend at least an hour a day preoccupied with perceived flaws, who experience resulting clinically significant distress or impairment in functioning, and who perform at least one associated repetitive behavior are believed to have BDD.

Patients who present with concerns about minimal or slight defects in appearance (e.g., asymmetry that would typically only be noticeable to a trained professional) should be carefully assessed. In cases where patients present with minimal or slight defects in appearance, the degree of distress they are reporting and the amount of functional impairment they are experiencing can help differentiate those with and without BDD. For example, a patient who is so concerned about a minimal or slight defect that (s)he refuses to attend school or leave home likely meets criteria for BDD. In contrast, a patient with a minimal defect who reports feeling self-conscious in some situations but is otherwise functioning well most likely does not have BDD.

Patients with BDD are often secretive about and ashamed of their concerns and the extent of their preoccupation and distress. In our experience, some patients purposely minimize their symptoms in the hope that the surgeon will not discover that they have BDD and refuse to operate. As discussed above, it is not uncommon for BDD to go undetected by aesthetic surgeons or dermatologists who offer cosmetic treatments. The majority of aesthetic surgeons and dermatological surgeons have reported that they have had the experience of operating on a patient only to recognize, during the postoperative course, that the patient had BDD.^{116,117}

There are a number of other behaviors that may suggest the presence of BDD or other significant psychopathology. In general, patients should be able to discuss specific appearance concerns that are readily observable. Patients who present with vague, nonspecific complaints (e.g., comments about being ugly or deformed, “my jaw just doesn’t look right”) may have BDD. Patients who express beliefs that other people are taking special notice of them because of their appearance “defect” may have BDD. Other individuals may make repeated requests for reassurance about the perceived flaw, which may signal the presence of BDD. Some patients with

BDD bring drawings to the consultation that detail how they would like to change their appearance or photos of celebrities to illustrate their idea of perfection; such behaviors may indicate the extensive amount of time they spend obsessing about their appearance. Patients who have had multiple procedures on the same body part yet still express dissatisfaction with treatment outcomes may have BDD. Those who have had many previous cosmetic procedures should be carefully queried about their satisfaction with the prior procedures, the nature of their appearance concerns, BDD symptoms, and expectations for treatment outcomes.

The degree and psychosocial consequences of dissatisfaction also should be assessed. Asking the patient about the amount of time spent thinking about a feature or the activities missed or avoided may indicate the degree of distress and impairment a person is experiencing and may help determine the presence of BDD. Self-report measures of BDD symptoms, such as the BDDQ, also may be helpful in this regard.

If the surgeon suspects that a patient has BDD, he/she is encouraged to inform the patient of their impressions and to provide some brief education about the disorder (e.g., “It sounds like you have a body image problem known as body dysmorphic disorder, a known and treatable condition”). We also recommend that surgeons inform patients with suspected BDD that they are concerned that the patient will be dissatisfied with the outcome of the surgery and that cosmetic procedures rarely help BDD symptoms, and can in fact make them worse. Then, patients should be briefly made aware that there are effective treatments for BDD, including psychiatric/psychological treatments, and referrals to a psychiatrist and/or psychologist can be made. It can be helpful to provide patients a list of local mental health providers with expertise in BDD or other body image problems and to convey to the patient that effective mental health treatments are available.

A major challenge in making such referrals is the poor or absent insight that is typical of BDD. Patients may resist the diagnosis because they believe that they truly are ugly. It can be helpful for surgeons to note that there is a mismatch between how people with BDD see themselves compared to how others see them, for reasons that are not well understood – that individuals with BDD see themselves as ugly or deformed, whereas other people do not see them this way. It is not helpful, however, to argue with the patient about how they look or to try to convince the patient that you are right and they are wrong, as this is likely to be ineffective. In our experience, it is more helpful to empathize with and underscore the patient’s distress and the impact of their appearance concerns on their daily lives (e.g., “I can see how worried you are about your jaw and how much it’s upsetting you and interfering with your life”); this approach can be helpful in encouraging patients to accept a mental health evaluation and treatment.

In general, it is best to be clear about why a referral to a mental health provider is being made (to get effective treatment for BDD) and not to promise that surgery will be performed after the psychiatric evaluation. It is best not to minimize the patient’s concern (e.g., “It’s all in your head”), provide reassurance that they look okay (unless the patient recognizes this to some degree themselves), or say something like “Well, I see a little something, but it’s not that bad”; these strategies are unlikely to be helpful and may even exacerbate the patient’s distress. Surgeons are also discouraged from

giving in to requests to perform minor procedures or to offer less invasive treatment options to appease the patient,³⁰ as in our experience patients may have a poor outcome following even minor interventions. Referrals to other surgeons are also discouraged, as this gives patients the implicit message that surgery may be helpful when in fact it appears unlikely to be.

Observing office behavior

Physicians and their staff should pay attention to patients' behavior in the office. Deviations from expected, typical behavior may reveal clues about BDD or other psychopathology. Demands for unusual appointment times (e.g., in the evening or early morning), repeated cancelling and rescheduling of appointments, excessive phone calls, angry or threatening demands to speak with the surgeon, or repeated reassurance-seeking from staff about their appearance may be indicative of BDD. Surgeons may be unaware of these behaviors, particularly if patients are "on their best behavior" during their consultation in hopes of convincing the surgeon to perform the desired procedure. Surgeons can consider asking patients to return for a follow-up consultation if the office staff raise concerns. A mental health evaluation is recommended if concerns about the patient's behavior persist.

General considerations

A mental health professional can be a valuable consultant to an aesthetic medicine practice. The mental health professional should have a good understanding of the psychological aspects of aesthetic medicine, as well as knowledge of disorders with a body image component, such as BDD and eating disorders. In most cases, the mental health professional will be called upon to assess a patient's psychological appropriateness prior to and for a given procedure. The mental health professional also may be asked to consult on the care of a patient postoperatively. This is most likely to occur in situations where the patient is dissatisfied with an objectively successful outcome or when the patient experiences a significant postoperative complication and is experiencing emotional distress.

Regardless of the circumstances, aesthetic surgery patients may react to a referral to a mental health professional with

anger and defensiveness, believing that they will only feel better if they look better. Others may assume that the medical professional assumes they are "crazy". Many will likely refuse to go to the consultation, which can provide indirect, confirmatory evidence that a patient is not psychologically appropriate for surgery. To increase the likelihood that the patient will accept the referral, it should be treated like a referral to any other health professional. The patient should be informed of the specific areas of concern and the reason for the referral. This information also should be shared with the mental health professional in advance of the consultation.

Conclusion

Interest in the psychological aspects of cosmetic medical procedures has grown in parallel to the overall popularity of the treatments. While early clinical reports from this literature suggested that most patients presented for treatment with some form of psychopathology, more contemporary and methodologically rigorous studies have identified few differences between individuals who seek cosmetic treatments and those who do not. Perhaps the most consistent difference is that those women and men who seek cosmetic treatments report higher levels of body image dissatisfaction. This dissatisfaction is believed to motivate the pursuit of treatment and improve following improvements in appearance.

Unfortunately, some individuals present for cosmetic treatment with extreme body image dissatisfaction. This dissatisfaction is a hallmark characteristic of both eating disorders as well as body dysmorphic disorder. Between 5% and 15% of persons who seek cosmetic treatments are believed to suffer with BDD; unfortunately, few experience improvements in their symptoms following treatment, leading to the belief that BDD is a likely contraindication to cosmetic treatment.

For these and other reasons, plastic surgeons and other physicians who offer cosmetic treatments are encouraged to evaluate the psychosocial functioning and status of new patients. Assessment of motivations and expectations for treatment, body image and appearance concerns, as well as psychosocial status and history can identify patients who may be inappropriate for treatment. Such assessment can also help to insure that the largest number of patients experience their physical as well as psychosocial goals for treatment.



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The role of ethics in plastic surgery

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SYNOPSIS

- Ethics as seen by professional associations.
- Ethical relationships with patients.
- The ethics of advertising.
- The role of ethics in the outpatient office.
- Ethics in the operating room.
- Ethical relations with other providers and third-party payers.
- The ethics of expert witness testimony.
- Summary.

The subject of ethics pervades the specialty of plastic surgery. Ethical decisions are highly prevalent in its practitioners yet few realize they confront these choices regularly, almost daily. Behaving in a morally responsible fashion, maintaining high personal codes of conduct, and remaining competent in operations are noncognitive functions for the vast majority of surgeons; it is deeply ingrained in the psyche. It also serves the surgeon well in presenting an overall highly regarded and deserved reputation amongst colleagues and the public.

Who to operate on and, more importantly, who not to operate on can in many instances be dilemmas that require moral choices. But many times the rationale is played out in the surgeon's subconscious, one more decision out of dozens made daily, with just a few moments to evaluate the alternatives. Plastic surgeons do not go home to their spouses every night and claim they made a number of highly ethical choices that day. Yet in reality the effects of not making the right choices can set up traps and entanglements. Breaching unwritten and written moral codes may bring consequences in this specialty. The harm may be done to others. The fallout is usually the surgeon's predicament.

Consider this common scenario. A patient consults the plastic surgeon for a rhinoplasty, complaining of poor breathing and an old fracture. She also doesn't like the shape of the

tip of her nose. She claims she has no money for any private payment of the fees involved. But she also claims to have over a half-dozen friends who want their noses changed and states she will take them to meet the surgeon on each of her subsequent visits. The surgeon agrees to charge her insurance company for the entire procedure, hoping in the end to capture more business from the friendly and social patient, deciding it is a justifiable prevarication. Is this an ethical dilemma?

The moral issues of this story become a web of further entanglement when the insurance company suspects it paid for a portion of the surgery that was cosmetic and not functional. A few months later the patient receives a denial of payment from the company for what they have determined is the cosmetic portion of her anesthesia charges, the facility fee and surgeon's fees. She is suddenly required to pay a sizable amount of money and in turn begs the surgeon to write off the balance since she still cannot afford to make up the difference.

Did the surgeon commit fraud? Was his decision to further his practice by committing a deception immoral? If he refuses to let the patient off the hook financially, will this affect his reputation with her friends who are by now signing up for their own surgery? Even if he made the very first decision that led to this predicament casually he cannot easily make this last choice without some degree of moral calculation.

Consider another situation. A 65-year-old uninsured diabetic is hit by a bus and suffers a compound tibia-fibula fracture and degloving injury of one-third of his lower leg. He is a smoker and is insulin-dependent. After the fracture is stabilized the plastic surgeon is asked to consult on the case for soft-tissue coverage of the sizable defect. Knowing that the zone of crush injury is extensive and there is compromised blood flow to the lower leg, the surgeon must decide if a long and expensive operation with a modest but very real chance of being unsuccessful is worth the effort and cost. With an amputation below the knee the chances this man will ambulate in a prosthesis are good, but not guaranteed. Will

prolonged recovery from a valiant limb salvage operation be the better choice? The surgeon knows he will not be reimbursed well for his efforts. His decision, if made on high standards, is based on what is right for the patient, not the surgeon.

These types of choices are encountered in similar situations on a daily basis by plastic surgeons all over the country. How one deals with these types of scenarios is multifactorial, complex and requires sophisticated decision trees. It is not immoral or unethical to say no in these situations.

Highly ethical persons have a well-developed internal moral code. They conduct themselves accordingly and believe that to do anything less would make them guilty of immorality. Contrast this with a sociopath who has no capacity for guilt, makes choices that he knows will deliberately harm others and then denies responsibility for the consequences. People living at the opposite extremes of this spectrum are rare. Most of us fall somewhere in between, the angel on one shoulder and the devil on the other.

Surgeons are themselves no different even though they have all supposedly taken the oath of Hippocrates to “above all else, do no harm”. The training of surgeons results in behavior that is consistent with the moral character of the role models the surgeon learned from, in both a positive effect and a negative one, sometimes full of awe, other times full of loathing. The behavioral end result of this training is a hybrid of choices, instincts, and internal codes that is rarely monolithic. More often the surgeon who has trained hard for a subspecialty designation is a complex, principled individual with a great capacity for a wide variety of mostly predictable and virtuous behaviors.

The specialty of medical ethics comprises a wide range of subjects that is considered valuable for physicians to consider and be knowledgeable about. It also takes into account the effects surgeons can have on society and vice versa. This includes controversial issues such as whether or not society should allow late-term abortions, death with dignity, or rationing of expensive treatments, to name a few. In general, the literature in medical ethics contains very little on the subject of plastic surgery.

In the lay literature, the ethics of having one's appearance altered is a somewhat more common, but still rare, subject. Feminists weigh in on this topic most frequently, as do PhD candidates in the fields of sociology and behavioral psychology.¹⁻³ Yet these dialogues do not take into account the possibility that the surgeon has high moral standing. Instead the plastic surgeon is cast as a villain, forcing his or her susceptible patients into paying more than they can afford for quite frivolous reasons. The patients are defined as foolishly chasing an impossible-to-obtain god-like appearance, involuntary victims of society's fascination with attractiveness. A further subtheme of these publications is the speculation that widespread alteration of homely persons into attractive ones will in the long term breed out common sense in our society.

The specialty journals in reconstructive or cosmetic surgery rarely, if ever, contain purely ethical articles of interest to the plastic surgeon.⁴⁻⁶ There are, for now, no ethical courses one can take at medical symposia, and forums on the subject of ethical plastic surgery are unheard of.

Yet the fact remains that ethical decisions are quite common in the lives of plastic surgeons, in some cases occurring even on a daily basis.

Ethics as seen by professional associations

The American Society of Plastic Surgeons (ASPS), the largest membership organization in the specialty, was formed in 1935. The association's attempt at a written Code of Ethics was first published in 1980. Members in good standing are expected to be familiar with this code and to adhere in their daily practice of surgery to the standards espoused within it. Failure to adhere to the guidelines can result in disciplinary action, including expulsion.

The expectations for ethical behavior on the part of members of the professional association are strongly worded and very specific. At times the code has been modified to meet new challenges such as those posed by the internet, charity raffles, and expert witness testimony. All realms of the specialty are covered within its dictums. The code also clearly spells out how a member will be dealt with if there is perceived to be a violation of the rules of the code.

Other members, patients, and lay persons can all lodge a written or verbal complaint with the ASPS Ethics Committee, stating what they think may be unethical behavior on the part of the member, actions that fall outside the proscriptions of the code. The member is then investigated by his or her peers and if it is decided that a violation did take place, the information is then passed along to the Judicial Council. The Council, comprised of members voted into that position, holds hearings to determine if sanctions should be placed on the member. Personal appearances before the Council are welcomed and the decisions made after a hearing are binding. Appeals of these decisions can be made to the Board of Trustees of the organization but are done infrequently. Plastic surgeons who are members of the American Society of Aesthetic Plastic Surgery (ASAPS) are subject to the same Code of Ethics and discipline. Members in good standing of both organizations may be elected to hold positions on the Ethics Committee and the Judicial Council for a period of 2–3 years.

Table 4.1 is a compilation of the data available from a review of the ASPS Ethics Committee's activities over the 4 years from 2006 to 2009.

While fewer complaints have been lodged lately, down to 81 in 2009 from 139 in 2006, the number of complaints that are reviewed after a committee investigation remained stable over this same period. Likewise the number of reviews that led to a hearing stayed at the same level, as did the number of hearings that resulted in disciplinary action.

Table 4.1 American Society of Plastic Surgeons Ethics Committee's activities, 2006–2009

Ethics complaints	2006	2007	2008	2009
New complaints	139	131	114	81
Complaints dismissed	101	77	54	36
Cases reviewed	38	54	60	45
Referred to Judicial Council	10	15	18	15
Cases disciplined	5	9	8	8
Complaints closed	153	129	108	84

Table 4.2 Average complaints by category per year, 2006–2009

Advertising	50
Medical board discipline	20
Contest	11
Standard of care	12
Expert witness testimony	10
Professional misconduct	6
Exorbitant fees	3
Criminal charges	2
Expert report	2
Total	116

Table 4.2 reveals the average number of complaints by category over the 4-year average. Advertising interpreted to violate the Code of Ethics has remained the complaint with the highest frequency over many years. The second highest category remains the investigation of those members who have been sanctioned by their state medical boards. The third category, unethical behavior while participating in a contest where the prize is free surgery, remains controversial. Some members feel that promoting themselves over nonmembers who are self-designated cosmetic surgeons is necessary to compete for potential patients and that this portion of the code is too restrictive. Still others feel it adequately reduces the number of violations of the code and reduces behavior that besmirches the reputation of all plastic surgeons. This controversy is unlikely to end soon.

Plastic surgeons overall have a highly visible position in the medical profession. Reactions to unethical behavior can thus be intense and scathing. For this reason members of the ASPS and ASAPS are reminded from time to time to review their Code of Ethics. While the vast majority of members will never in their careers be accused of violating it, pleading that you had no idea your actions were directly opposed to the body of rules for conduct in the code never works well as a defense when confronted by this system.

Ethical relationships with patients

In an ideal world plastic surgeons would only meet patients for consultations that were precisely matched to their skills, with the perfect indications for only the operations they preferred to perform. The surgeon would immediately comprehend the correct desires of the patient, infallibly interpreting that person's own unique ability to deal with a complication or a less than desirable result. The surgical results would always heal immediately with no complications. The adoring patient would then refer many more patients just like themselves.

In reality things are rarely clear and perfect. Patients fret about what they will look like after cosmetic surgery; they worry hopelessly before reconstructive surgery that they will still end up looking deformed and disfigured. They fritter away the surgeon's time with endless questions about whether or not they should have the surgery. Then they present impossible impediments to surgery scheduling and are often unrealistic about their recovery, postoperative pain, and activity

restrictions. In a busy, demanding practice, how surgeons take control of these situations, occasionally to their own advantage, can sometimes lead to unethical decision-making. Taking the high moral ground, while always the best choice, can sometimes seem impractical and intrusive when demands on the surgeon are almost overwhelming.

When a surgeon's compensation is determined solely by the number of surgeries he or she can perform in a week, a month and a year, operating on a person ill-suited to the surgery can possibly, perhaps eventually, occur. Some surgeons claim only to operate on patients with whom they feel comfortable. Obviously they have the luxury of dismissing patients they don't like and have a practice of truly elective procedures only. Being financially rewarded from performing surgery on people with unrealistic expectations, who may be ill-suited emotionally for the end result, is not the norm in this specialty. Yet it does occur, perhaps too often.

The consequences of this, an upset patient who abhors the result and threatens lawsuits or reports to the media, will in most cases lead to regret, the surgeon ruing the day he or she laid the scalpel to that person's skin. But it does not necessarily guarantee the surgeon has learned to be more careful from the experience.

In the training of plastic surgeons, being grilled over and over from the elder surgeon as to the correct indications for surgery is common. The master surgeon feels he or she is there to teach future surgeons the unwritten rules, the pitfalls of making the wrong choice, and the integrity required to succeed in the specialty. Once in practice, however, new surgeons no longer have to answer for their every action. The guidance for making the right, not the wrong, choice is up to them alone, and the consequences can lead to an unhappy patient, a profound effect on their reputation, disciplinary action or, most unfortunately, malpractice litigation.

So it is that surgeons are ultimately judged by the "standard of care", what a reasonably prudent surgeon would do with similar training in similar circumstances. Moral and ethical behavior is one facet of the standard of care.

Truly ethical surgeons choose their patients based on a thorough evaluation that includes many factors, compensation being the least important. Patients with unrealistic expectations or obsessive behavior are dismissed appropriately. Patients who need reconstruction are chosen on the surgeon's ability to match the correct operation to the problem. Patients with needs beyond the surgeon's own particular skills are referred to others who have more expertise in that area.

Society expects that conventional and virtuous surgeons spend time teaching their patients what their expectations should be both for the less-than-perfect result and for unfortunate but rare complications. The option to dismiss the surgeon or seek another one once patients know the risks and alternative treatments should always be allowed. This is accompanied by a disclosure of how much financial responsibility the patient must bear for reoperations when things do not go as planned and another operation is needed.

In reconstructive surgery, patients' ability to pay or the type of insurance coverage they have does not affect the ethical surgeon's decisions to operate. The complete lack of insurance is balanced by the ability to find some type of payment coverage through social services or simply accept a very reduced fee in exchange. The need for the operation should not be



Fig. 4.1 Unethical advertising – billboard photo: “two for one.”

altered by the compensation that will result, especially if it is little to nothing at all.

The ethics of advertising

Advertising was considered completely unethical for plastic surgeons well into the 1980s. A few who tried it were considered outlaws and often expelled from their national or state and local plastic surgery associations. Many felt it “cheapened the specialty” and that reputation was all that should be needed to attract more patients.

Along came the 1990s and the social attitudes of the specialty changed. Television discovered plastic surgery and shows like *Extreme Makeover* thrust plastic surgery into the homes of millions, making “mommy makeovers” a household word. But it was the internet that tore down the last bit of reluctance to make promotion a major part of the everyday practice of plastic surgery.

Advertising in the specialty, when done in good taste and without hyperbole, will now be around for a long time. Unfortunately unethical advertising, done in poor taste with mind-numbing self-promotion, is also here to stay (Fig. 4.1).

The ASPS Code of Ethics has been modified several times in the last dozen years to keep up with the changing relaxation of social mores to physician advertising. But complaints from members about other surgeons’ unethical promotions continue to rank as the most frequent complaints each year to the ASPS Ethics Committee (see Table 4.2).

Examples abound. Fig. 4.2 is exactly what the Code of Ethics was meant to prevent: a rather tacky approach that cheapens and sullies the specialty regardless of the origin. The public lumps all plastic surgeons into one category, whether they are Board-certified or self-designated.

Showing misleading before-and-after photos, then implying this to be a typical result that can be obtained by any patient, is considered unethical as well (see Fig. 4.2). In addition, the temptation to airbrush imperfections or scars out of the photos can be hard to resist when software applications

abound that make this an easy task. Any altering of before-and-after photos is considered by the ASPS ethics process to be false and misleading advertising, subject to sanctions.

Other behaviors considered to be unethical include the trading of surgery *quid pro quo* for media exposure in a high-profile person. Examples unfortunately exist of television figures such as news reporters undergoing surgical treatment in return for free testimonials about the surgeon, on air or at public appearances. While the media industry doesn’t consider this out of the ordinary, plastic surgery associations maintain that it is in fact unethical.



Fig. 4.2 Unethical advertising where a single image is used for both before and after figures through the magic of digital alterations.

The role of ethics in the outpatient office

Building and maintaining relationships with patients and staff can occupy a good deal of the plastic surgeon's time. The temptation to extend those relationships outside the office or the practice and outside a professional nature will always be present. Grateful patients wish to offer favors in exchange for their surgeon's success. Adoring staff members want to know more about what their boss is like outside the clinic. It is only natural for attractions such as these to take place. How the surgeon handles this can make him or her more successful, but can also lead to situations that can become unconventional, complicated, and entangling.

While it is not considered unethical to socialize with one's staff, establishing sexual relationships with staff and patients violates general standards for professional conduct, and can end with unfortunate consequences, including charges of sexual harassment or other civil charges. Lecherous behavior, physical advances, and the creation of a sexually harassing environment are grounds for dismissal from professional organizations, civil lawsuits, and can even at times be considered criminal in nature.

Conventional behavior sets limits on these situations. But the unique situation in plastic surgery, where the female patient may be both physically and emotionally exposed, can create powerful forces that test the limits of decency, honesty, and virtue in male plastic surgeons. To a lesser extent the opposite gender roles can also occur, as women are becoming plastic surgeons at record rates.

Personal standards of conduct vary tremendously in the specialty, but television shows depicting sleazy, illegal, and unconventional behavior by plastic surgeons may have some element of truth. The malevolent, licentious, and perverse personality in some surgeons may in fact be portrayed in these situations. Hopefully this will remain rare and only in the purview of television. Brazen behavior may eventually be reported to some type of authority. The potential personal damage that can be done in these situations by and to surgeons should be deplorable to all.

Attorneys experienced with workplace lawsuits always recommend that, if a romantic relationship develops between a patient and a single physician, the patient must be given the choice of terminating either the doctor-patient relationship or the personal relationship. If the first choice is made the patient should submit to being discharged from the surgeon's care to another physician. Likewise, if a romantic relationship arises with staff members it is considered ethical and wise to discontinue the employee-employer relationship immediately, though the evidence suggests this happens infrequently.

The plastic surgery practice with multiple physicians presents the possibility for competitive economic and unprofessional behaviors amongst surgeons and staff. Manipulation of the staff to hinder the success of partners or to direct more business to oneself is considered unethical. Hiding income from expense-sharing agreements, contributing to rumors and lies about other partners, and other obtrusive and malevolent behaviors towards them ignore the rules of decency and virtue.

Ethics in the operating room

The outcomes of any surgery depend on the correct application of principles, decisions, and treatments, all of which require multiple informed and decent choices. How the surgeon conducts himself, resisting the temptation to blame others and even the instruments when things do not go as planned, affects his reputation amongst staff and colleagues. Each correct or incorrect decision made during surgery can be a reflection of the character and mores of each surgeon.

Cutting corners for economic reasons, covering up mistakes, and delivering different outcomes than planned may be fundamental indications of a dishonest character. Surgery is not immune to the effects of personality flaws.

The analogy of the old fairy tale by Hans Christian Andersen, *The Emperor's New Clothes*, to the potential for deceitful behavior occasionally exhibited by plastic surgeons can be illustrative. In the story, the weaver promises to make the emperor a set of clothes invisible to those ignorant or unfit for their positions, completely fooling him into wearing nothing. It is a classic case of "mind over matter".

To the extent this can be applied to plastic surgery, the limited effects of some surgery may depend on the extent to which the surgeon built up the patient's expectations, knowing full well that the patient had paid for something possibly requiring more time and effort or that might have had a more clearly effective result. While this is rarely as brazen as in the old fairy tale, it can slip into various parts of surgery, especially with the more common use of treatment machines the patients know little about. The happiness of the patient depends on the expectations for beauty woven into the sales presentation by the surgeon. Results will vary of course.

Certain energy-dependent skin treatments whose effects take many months to be appreciated parallel this story. Is it dishonest to promise fewer wrinkles when it is known the effects won't be as plainly evident as other treatments or as a more expensive surgery? When the frequently pricey payments on the machine need to be met, the temptation to oversell it can be enormous. The ethical dilemma is not just to sign reluctant patients up but also then to deny that the outcome was less effective and did not meet their expectations.

Conventionally moral surgeons recognize this trap and avoid it, choosing to defer income for traditional effectiveness. Others, who might still consider themselves to have mainstream values, nonchalantly overlook the issues for the sake of keeping busy, building their reputation and impressing other surgeons with the size of the practice. Willful and malevolent deception may not be in the forefront; mostly it is hidden, buried in this specialty behind layers of complex situations. But it certainly exists in many forms.

Ethical relations with other providers and third-party payers

The ASPS Code of Ethics is very specific about the pitfalls in monetary relationships that can exist in referral networks. Brazen kickbacks for referring a patient for whom the surgeon will be rewarded financially are considered illegal in most states. Fee splitting is as well. With Medicare it can become a

federal offense. More subtle alignments and *quid pro quos* with the referring physician may not constitute civil violations but nonetheless should be considered carefully as a possible ethical violation before being carried out.

Correctly applying Current Procedural Terminology codes which accurately and adequately depict the procedure that was performed is presumed to be the norm in surgery. Yet constant tension with third-party payers over what can be interpreted as their unjustified decreased reimbursement for procedures requiring high levels of skills creates a negative attitude that can pervade the business side of the profession.

When it is assumed the insurance company “cheated” the surgeon on the last payment, the temptation to overbill the next procedure is difficult to resist. Is it justifiable to “unbundle” codes, upcode, and overbill when one knows that the insurance company has the upper hand anyway? Who is really harmed by this? It is situational ethics in play: the seemingly acceptable deception that is justified because everyone else, including the payers, is playing the same game.

Much has transpired over the past 5 years as several large insurance companies have been taken to court in class-action lawsuits for unlawful changes to the billings of physicians. Their reply is that fraudulent surgical billing is rampant and they have to protect their bottom line. The truth may lie somewhere in between. Nevertheless, the real world seems to forgive physicians tempted to push the envelope of honor and conduct for now, given the intense fiscal realities. Patients may abhor what they hear about hospital billing, but forgive their own surgeon if he seems honest and caring. The more personal this becomes, the less patients consider it greed if it seems to be in favor of a surgeon who did a successful procedure on them.

On the other hand, in university teaching hospitals, where an attending surgeon is expected to supervise the training of many residents, there were in the past submissions of surgeon’s fees for being in two places at once, or even not present at all. The explanation was that as a teaching surgeon the physician was ultimately responsible for all of the outcomes and therefore justified in receiving the compensation. Some well-publicized record fines from the Centers for Medicare and Medicaid in the last decade have led to very strict rules for supervision and billing. Unethical billing is now scrutinized more closely than ever and the plastic surgery team may not be an exception. Obtrusive rules may have constrained the system and possibly gone beyond reason. Unfortunately they now exist because of the past abuse of the system by a very few.

The ethics of expert witness testimony

As in other sections of this chapter, once again, the issues outlined in the ASPS Code of Ethics are applicable here as well. Usually one of the most frequent complaints brought against a surgeon by another member of the ASPS is for testifying either in deposition or at trial in a manner that can mislead the jury or simply be out and out contrived of false statements of fact. Many of these complaints center around the expert declaring that the standard of care was to do the surgery in a specific fashion. In fact, however, many surgeons may not adhere to those same principles and perform the surgery differently, but not necessarily outside the standard.

Condemning one way or the other as not in alignment with accepted principles when in fact it may very well be, can swing the jury or judge to rule against the other member. Regardless of the outcome the member who has a legitimate issue can submit the testimony he or she feels was false or misleading to the ASPS Ethics Committee who will review the situation and arrive at a conclusion.

The Code of Ethics is also very specific about the expert’s reasonable experience with the surgery that was performed. The phrase “recent and substantial experience” needed to be more carefully defined because of retired surgeons’ declarations of the standard of care when in fact they may have not performed any surgery, let alone the one in question, for over a decade. As the code is written now this means within the last 3 years. Testifying about a procedure the surgeon has not performed then in 4 or more years can be considered misleading testimony.

Overall, these issues became such frequent complaints that multiple other modifications to the Code sections on testifying have had to be made. This now includes a declaration that all experts may be asked to sign, certifying they will be truthful in their testimony. The submission of the signed statement is voluntary but can be used as evidence in the courtroom, especially when a plaintiff’s expert is another member of the ASPS and has been known to have made misleading statements in other trials.

The ethics of physical or chemical impairment

As surgeons age they need to maintain both their mental and physical health. When hand–eye coordination changes with health and age, who is to judge the standards for ethical patient care when results are substandard due to unmanaged tremors, slipping dexterity, declining eyesight and weakened coordination among other physical effects of aging? Most surgeons can recall a mentor or friend who carried on despite these subtle changes who perhaps should have heard the call to stop operating before it became an issue with detrimental results. Similarly, however, many can recall a mentor who carried on with no changes to his or her surgical skills well into their ninth decade.

Choudry⁷ did a systematic review of 62 studies that related medical knowledge and healthcare quality to years in practice and physician age. Some 52% of these showed decreasing performance with increasing years in practice for all outcomes assessed.

Institutions vary greatly in their standards for the aging surgeon, but when much of plastic surgery is carried out in one’s own office, there is little to no oversight or governing body to control these issues.

The demands of plastic surgery where tolerances for error are measured in millimeters cannot be compared to, say, one’s driving skills or golf game. Only when one becomes a danger to others on the road or the course will these freedoms be taken away.

So the ethics of aging and carrying on beyond a reasonable time to retire can become acute when others know the truth.

Plastic surgeons who are truly ethical will always question their results, their ability to learn and grow and their own quality of care. Warning signs that these questions are not

being dealt with truthfully or that the surgeon may need a reality check include increasing complications, decreasing patient satisfaction with their results of surgery and mounting malpractice cases in addition to all of the above.

Beyond that is the issue of the silent colleague who is witness to incompetent surgery or impairment. For surgeons there has always been the fear that “turning someone in”, especially someone who was at one time highly skilled, will result at some point in recriminations from other surgeons in the hospital for doing so, either overtly or more often covertly. Walking the thin line between wishing to act on an errant surgeon but finding such action too unsavory does no one any good. Alternatives, however, exist to this onerous task and the hospital itself is morally responsible to act, with channels for privilege restrictions being commonly used.

The specialty, however, frequently operates well outside of the discipline provided by hospital privileges, especially when one owns their own surgical suite and is subject to no higher authority. Sadly, then, the end of an era in some surgeons’ career has come when malpractice issues pile up and obtaining insurance becomes too costly to continue or even nonavailable. Why wait until this tragedy occurs?

Chemically impaired physicians exist in this specialty as well, since we often are second only to anesthesiologists in terms of access to narcotics, benzodiazepines and other such abused medications. The impaired surgeon typically has gone to great lengths to protect their covert use of both drugs and alcohol from colleagues; even those closest to the impaired surgeon in the same practice relationship are usually unaware of the extent of the problem. Respondents to a recent AMA study⁸ met diagnostic criteria for impairment at the rate of 12.9% of male physicians and 21.4% of female physicians.

What therefore is ethical for the plastic surgeon who finds out the truth about a colleague but has a sense that acting on it will cause more harm than good? Moral principles must then override all other consequences, financial resources and friendships.

When patient care is compromised by impairment we all have the duty to intervene whether we find it distasteful or frightening. Avoiding the truth is just as unethical as the act itself of abusing substances that are too readily available.

Summary

The practice of medicine is complex, requiring constant decisions, discussions, and testing. How this plays out in the daily

lives of plastic surgeons depends on their background, training, personal mores, and interpersonal skills. Unethical behavior can range from pushing the envelope in insurance coding and billing, all the way to fraud, sexual deviation, and the cover-up of surgical misadventures. It is a pervasive issue that can be seen as either business as usual or a moral stance always to behave ethically. Human nature being what it is, the give and play between highly ethical behaviors and the alternative will always be a part of the specialty.

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Business principles for plastic surgeons

C. Scott Hultman

SYNOPSIS

- This chapter provides a broad overview of the essential principles that characterize what a business does and how a business does its work.
- The ability to apply business concepts is of paramount importance if plastic surgeons are to become and remain leaders in healthcare.
- Plastic surgeons should understand and use strategy, accounting, finance, economics, marketing, and operations to help guide decisions about their practice.
- Innovation, entrepreneurship, and human resource management are three areas where plastic surgeons can add value to their practice and distinguish themselves from their competition.

Introduction

"Make everything as simple as possible, but not simpler."

Albert Einstein

Not only is healthcare business, it is big business.

The healthcare-industrial complex incorporates multiple sectors to deliver health and depends on an expanding group of interdisciplinary teams, services, and institutions to achieve this value proposition. Business sectors involved in the delivery of healthcare include not only professionals such as doctors, nurses, and administrators, but also hospitals, nursing homes, and home healthcare groups; drug manufacturers and developers; manufacturers of medical equipment and instruments; diagnostic laboratories; biomedical researchers; and biotechnological entrepreneurs.

Current estimates by the Office of Economic Cooperation and Development place healthcare spending at 17.9% of the United States' gross domestic product, with that percentage expected to increase to 19.5% by 2017.¹ For every dollar spent in the US on healthcare, 31% goes to hospital services, 21% to physicians, 10% to pharmaceuticals, 6% to nursing homes, 4% to dental services, and 28% to other categories, such as

diagnostics laboratories, medical equipment, and medical devices. Of note, 7% of total spending is assigned to administrative overhead costs.

If healthcare provided by physicians is not business, then physicians are certainly surrounded by business; they must navigate a complex environment that is full of paradoxes, inefficiency, and bureaucracy. Unfortunately, physicians receive no formal education in business but must learn on the job, through mistakes and successes, often one patient and one business problem at a time. Although many critics argue that healthcare has been tainted by the intersection with big business, which places the bottom line at the top and undermines the physician-provider relationship, many other thought leaders contend that healthcare needs business, to help solve problems of inconsistent quality, rising costs, limited access to care, and disparities in outcomes. Indeed, business thinking and business processes are desperately needed to transform our current system, so that healthcare can be available to all people, at fair-market prices, to improve the health of our community.

Why should plastic surgeons care about the business of healthcare? From an individual perspective, every plastic surgeon must either run a business or be part of a business, if the surgeon's practice is to thrive, grow, change, and continue to provide high-quality care. Whether one works for oneself, for a hospital or health maintenance organization (HMO), for an academic institution, for a non-profit or non-governmental organization (NGO), for a free community clinic, or for an overseas volunteer mission trip, plastic surgeons are involved with organizations that utilize business principles and interface with business entities.

From a broader perspective, however, plastic surgeons are uniquely situated to serve as leaders of healthcare systems and healthcare businesses. Given our extensive training, our collaboration with multiple specialties, our diverse portfolio of services that we provide, our problem-solving skills, and our entrepreneurial spirit, plastic surgeons have the leadership skills, influence, and positioning within the healthcare system to effect real change. Just as the Greek word *plastikos*,

which means to shape or to mold, was chosen to describe what we do as surgeons, this word could also impart upon us the ability to shape or mold our systems of healthcare delivery.

The knowledge and application of business principles is of paramount importance if plastic surgeons are to become and remain leaders in healthcare. The purpose of this chapter is to provide a broad overview of the essential principles that characterize what a business does and how a business does its work. Each section offers a topical overview, and readers are strongly encouraged to explore in more depth the following components of this chapter:

1. Strategy
2. Accounting
3. Finance
4. Economics
5. Marketing
6. Operations
7. Innovation
8. Entrepreneurship
9. Sustainable enterprise
10. Human resource management
11. Legal and regulatory considerations
12. Negotiation
13. Ethics
14. Leadership

The end of each section will spotlight an “Idea Watch,” as a forum to present novel, emerging, and occasionally controversial topics related to business and healthcare. Featured topics will be drawn from cutting-edge articles published in the *Harvard Business Review*, with the goal of promoting further reflection, analysis, and inquiry by the reader.

Plastic surgeons, at the very least, must learn the language of business, to have meaningful interactions with hospital administrators, insurance carriers, salespeople, and marketing firms. Hopefully, though, plastic surgeons can utilize the principles of business to improve the care that we provide, and in the end, to transform the industry in which we practice our science, and our art.

Strategy

“Long-range planning does not deal with future decisions. It deals with the future of present decisions... Significant competitive advantage lies with those organizations and individuals who anticipate well in turbulent times.”

Peter F. Drucker

Competitive advantage begins and ends with strategy (Box 5.1). Nearly all of the components of business are affected by strategy, from finance to operations, from marketing to managing human capital, and therefore a review of business principles should commence with an understanding of how strategy guides decision-making within an organization.

Strategy can be characterized as the art of inducing your competitor to do something else, while you focus on doing what you do well. In more academic terms, strategy is the process of forming, implementing, and evaluating decisions that enable an organization to achieve its long-term goals.

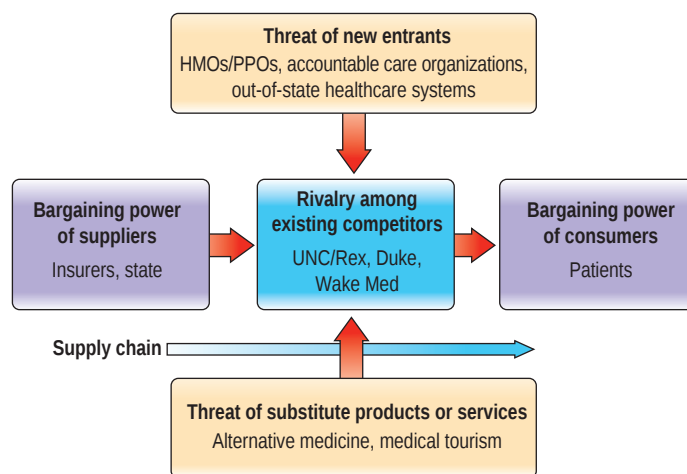


Fig. 5.1 Strategy: Porter's 5-Forces model of competition. HMOs, health maintenance organizations; PPOs, preferred provider organizations.

Strategy is dictated by (and, in turn, can influence) the organization's mission, vision, and values, which serve as a foundation to guide policy, projects, and programs. Furthermore, strategy is about competing on differentiation – creating a value proposition – in which a firm provides the consumer with a product or service of greater quality or at less cost than its competitor, deliberately choosing a different set of activities to deliver a unique mix of outputs.

Before examining specific strategic principles, one should become familiar with how the business environment affects the flow of inputs to outputs, along the **supply chain**. Because value is added at various points along this process, the entire axis, from supplier to consumer, is called the **value chain**. Primary activities of the company, which include inbound logistics, operations, outbound logistics, marketing and sales, and ultimately customer service, each create value that manifests in the final product; these processes are guided by strategic priorities and are coordinated by support activities that include technological development, human resource management, and firm infrastructure.

The most established and respected model of the business environment is Michael Porter's **5-Forces model of competition** (Fig. 5.1).² Each industry contains: 1) previously established competitors; 2) the potential for new entrants; 3) the threat of substitute rivals, who often compete on price; 4) suppliers, who can have significant bargaining power; and 5) buyers, who create demand for the outputs. Understanding the environment of a specific industry, such as healthcare, can strengthen decision-making and help with strategic planning. For example, how should an academic plastic surgery practice respond to the influx of recently graduated residents into the community? How should the solo private practitioner attract new patients in a fixed market, when a group practice dominates the landscape? How should surgeons challenge scope of practice with non-surgeon physicians and non-physician providers? What is the optimal portfolio of services, specifically the mix of reconstructive surgery, cosmetic procedures, and skin care, to achieve the goals of the organization?

Once the dynamics and landscape of the business environment are defined, specific decisions can be made regarding change in operations, marketing, investment in new assets, alliances, or supply chain.³⁻⁵ Most mature industries, such as the automotive industry or the personal computer industry,

settle into a competitive scenario in which one firm dominates with 60% market share, while a second firm contains 30% of the market share, and the remaining competitors occupy 10%. Because of barriers to entry, new entrants may not be able to successfully compete, unless disruptive technology lowers production costs or the market shifts, due to cultural, social, economic, or political forces. In fact, significant competitive advantage is conferred to small, nimble firms that focus their product line or services and offer a unique selling proposition, to a targeted segment of the market. When executed correctly, this activity, termed “**judo strategy**,” has the power to undermine dominant businesses and increase market share substantially.

A major limitation of competitive strategy is that most efforts deal with gaining a larger portion of a fixed market or attracting new customers via the “rising tide” of a slowly growing market. If companies in search of sustained, profitable growth compete with multiple rivals, then differentiation becomes difficult, price wars may ensue, and the total profit pool shrinks. Instead, companies may pursue a “**blue ocean strategy**,” in which uncontested but related market space is discovered, rendering rivals obsolete and generating new demand. Previous “settlers” will “migrate” to this new market space and become “pioneers.” Apple has done this over and over with the personal computer market, introducing new devices that expand the functionality of their operating system and hardware, evidenced by the transition from desktop to laptop to iPhone to iPad.

True value innovation comes when a company jumps out of their industry and creates an entirely new market, often in a different industry.^{6,7} This foray into uncharted territory, which is referred to as “**white space**,” typically occurs when a company develops a disruptive technology that permits the use of core competencies to produce a radically different product or service. Apple was successful in capturing the dominant position in the digital music market by designing and offering iTunes, despite being a computer company. Inherent to this success was the fact that Apple also changed the business model for purchasing music; consumers could buy singles or albums, listen to samples, and of course, use the website for free. As the music industry shifts again, from purchasing content to subscription services as a major revenue model, Apple is determined to remain the dominant player. The acquisition of the Beats music platform will allow Apple to compete with Pandora and Spotify, but also serve to stream video content for gaming and on-demand viewing of television and film.

In summary, strategy involves the following steps:

1. **Industry analysis** – assess industry profitability today and tomorrow
2. **Positioning** – identify sources of competitive advantage
3. **Competitor analysis** – study current competitors, future entrants, and substitutes
4. **Assessment of current strategy** – predict effectiveness and sustainability
5. **Option generation** – search for new customers, new segments, new markets
6. **Development of capabilities** – planning now for future opportunities
7. **Refining strategy** – assess uniqueness, trade-offs, compatibility with vision and values

BOX 5.1 Idea watch: strategy

Reference: Raynor ME, Ahmed M. Three rules for making a company truly great. *Harvard Business Review*. 2013;91:108–117.⁶⁵

How do great companies make great strategic choices? The authors studied 25,453 businesses, operating over a 44-year period, and identified several hundred that had exceptional, sustained performance. The decisions that allowed certain companies, like IBM, 3M, Merck, and Medtronic, to outperform their peers, followed three simple rules:

- Better before cheaper (compete on differentiators other than price)
- Revenue before cost (prioritize increasing revenue over reducing costs)
- There are no other rules (to change anything you must follow the first two rules)

These rules did not dictate specific behavior, or even general strategies, but instead served as foundational concepts, or guides, when making strategic decisions about acquisitions, diversification, resource allocation, and pricing. Competitive positions built on greater differentiation through brand, style, or reliability were more likely to drive exceptional performance than positions built on lower prices.

Accounting

“Nowadays, people know the price of everything and the value of nothing.”

Oscar Wilde

Business management must be based upon a common language that is used to objectively communicate information related to the quantitative metrics of an organization. That language is accounting (Box 5.2). This section will review the tools that accountants use to assess the financial health of a business: **income statement**, **balance sheet**, **summary of cash flows**, and **financial ratios**.^{8–10} The nuances of accounting are beyond the scope of this overview, but healthcare providers must have a basic comprehension of these instruments and how they represent the financial standing of their practice, their hospital, and their healthcare system. Furthermore, these instruments are used in budgeting to construct pro forma predictions of future performance.

The field of accounting is governed by generally accepted accounting principles, also known as **GAAP**, which are rules used to prepare, present, and report financial statements for various entities, such as non-profit organizations, publicly-traded companies, and privately-held firms. Although the government does not set these standards, the US Securities and Exchange Commission does require that public firms follow these rules. Managerial accounting, which is used to allocate cost and assign overhead, does not follow GAAP and is dependent upon institutional culture and practice.

Income statement

The income statement, also known as the profit/loss statement, describes financial transactions within a defined period of time, which may be quarterly or annually. Revenue refers to the gross income that a company receives from normal

business activities, typically the sales of goods or services, but may also include rent, dividends, or royalties. In accrual accounting, revenue occurs at the time of the transaction, not when receipts are collected. Net income is expressed as a profit or loss, after deducting expenses, which usually include operating expenses (cost of goods sold, variable overhead expenses), depreciation of assets and amortization of leases, fixed overhead (selling and administrative expenses, research and development), interest expenses, and taxes.

Revenue

less Operating costs

= Gross profit

less Fixed overhead

less Depreciation (assets) and amortization (leases)

= Operating income (EBIT)

less Interest expenses

= Pre-tax income

less Income taxes

= Net income

Balance sheet

The balance sheet is a snapshot of what the company owns and owes, at a single point in time. On one hand, the balance sheet summarizes the cumulative impact of all transactions, but the balance sheet does not provide much useful information on the operational performance of the firm. The net worth of the company, referred to as owner's equity, is defined as the difference between the assets and the liabilities.

Equity = Assets – Liabilities

However, balance sheets usually frame this relationship slightly differently, but again, the following equation must always balance:

$$\text{Assets} = \text{Liabilities} + \text{Equity}$$

or

$$\text{Assets} = \text{Debt} + \text{Equity}$$

The actual worth of a company, the equity, is difficult to ascertain, but one method to calculate value is market capitalization, which is (share price) $\times$ (shares outstanding); this represents the public consensus of the value of the firm's equity.

Assets are defined as resources with probable future economic benefit, obtained or controlled by the entity, as a result of past transactions, that are expected to contribute to positive net cash flows. Examples of assets include cash and cash equivalents (pre-paid expenses, bonds, stock), accounts receivable (the money that is owed but has not been collected), inventory (raw materials, work-in-process, and finished goods), property/plant/equipment (purchase price less depreciation), goodwill (intangible value of brand), and intellectual property.

Liabilities refer to what a company owes, or from a different perspective, how the assets were obtained. Liabilities

include short-term loans (credit lines) current portion of long-term debt, accounts payable (the money a company owes its vendors), and long-term debt.

Owners' equity – the difference between assets and liabilities – can be allocated into several categories: preferred shares (which usually receive periodic dividends), common stock, and retained earnings (accumulated earnings that have been reinvested into the business, instead of being distributed as dividends).

Summary of cash flows

An assessment of a company's cash flows is critical in determining the financial viability of the firm, because profit is NOT the same as cash. This disconnect is due to multiple reasons: 1) cash may be coming in from investors or loans; 2) revenue is booked at time of sale, not collection; 3) expenses are matched to revenue, not when they are actually paid; and 4) capital expenditures do not count against profit (because only the depreciation is charged against revenue) but require cash or debt to pay for the assets. As a result of this discrepancy between when a good or service is provided and when cash is exchanged, following the flow of cash can be very complicated. Fortunately, we have accountants. For mature, stable, and well-managed companies, cash flow does approximate net profit. But for younger, growing, and poorly-managed companies, profit can occur without gaining cash (resulting in bankruptcy, because bills cannot be paid) or cash can accrue without being profitable (which bodes poorly for long-term success, if expenses cannot be controlled).

Overall cash flows are further subdivided into three categories – operations, investing, and financing – based upon the conduit for the flow. Cash flows from operating activities (CFO) indicate how much cash was generated from operations: selling goods and services. Cash flows from investing activities (CFI) indicate how much cash the company spent (or received) from buying and selling businesses, property, plant, and equipment. Finally, cash flows from financing activities (CFF) indicate how much cash the firm borrowed, received from selling stock, or used to pay down debt or repurchase stock.

Total cash flow represents the true flow of money through a firm and is a composite of the operations, investing, and financing, represented by the following equation:

$$\text{Total cash flow} = \text{CFO} + \text{CFI} + \text{CFF}$$

Many financial analysts believe that total cash flow myopically focuses on earnings while ignoring "real" cash that a firm generates and retains for future investments. Therefore, another measure of the ability of a firm to create value is free cash flow (FCF), which is defined numerically as:

$$\text{Free cash flow} = \text{CFO} - \text{capital expenditures}$$

or alternatively:

$$\text{Free cash flow} = \text{net income} + \text{amortization} + \text{depreciation} - \text{change in working capital} - \text{capital expenditures}$$

In other words, free cash flow represents the total cash that a company is able to generate after laying out the funds required

to maintain or grow its asset base. FCF is very important to investors because this allows a firm to pursue opportunities that increase shareholder value. This is the best source of capital for development of new products and services, acquiring new companies, paying stock dividends, and reducing debt. Cash really is king, and this is why.

Financial ratios

Because companies even within a single industry can vary in size and maturity, such instruments as the income statement, balance sheet, and summary of cash flows may not permit a valid comparison of those companies. Instead, financial ratios – the numerical relationship between two categories – can provide powerful insight into the financial health of a company. Jonathan Swift observed that “vision is the art of seeing what is invisible to others,” and financial ratios provide that vision.

Four types of ratios help managers and stakeholders analyze a company’s performance: profitability, leverage, liquidity, and efficiency. These ratios can be used to follow the performance of a firm over time or to compare several firms across related industries.

Profitability ratios

Gross margin = gross profit/revenue

Operating margin = operating profit/revenue

Net margin = net profit/revenue

Return on assets = net profit/total assets
= (net income/revenue) × (revenue/assets)

Return on equity = net profit/shareholders’ equity

Contribution margin = revenue – variable direct costs
(technically not a ratio, but loved by CFOs everywhere)

Leverage ratios

Debt-to-equity ratio = total liabilities/shareholders’ equity

Interest coverage = operating profit/annual interest charges

Liquidity ratios

Current ratio = current assets/current liabilities

Quick ratio = (current assets – inventory)/current liabilities

Efficiency ratios

Days in inventory = average inventory /
(cost of goods sold [COGS]/day)

Inventory turns = 360/days in inventory

Days sales outstanding = accounts receivable/(revenue/day)

Days payable outstanding = accounts payable/(COGS/day)

property, plant, equipment (PPE) turnover = revenue/PPE

Total asset turnover = revenue/total assets

BOX 5.2 Idea watch: accounting

Reference: Kaplan RS, Porter ME. How to solve the cost crisis in health care. *Harvard Business Review*. 2011;89:46–64.⁶⁶

Stephen Kaplan, who engineered the concept of time-driven, activity-based costing, collaborated with Michael Porter, who introduced the idea of the value creation to supply chain theory, to develop a new model for determining the true cost of providing healthcare.

In the process, they identified 3 myths that needed to be challenged: 1) charges are a good surrogate for provider costs; 2) hospital overhead costs are too complex to allocate accurately; and 3) most healthcare costs are fixed. Kaplan and Porter proposed methodology to calculate the total cost of patient care, based on blending the cost of resources needed to provide care, the time needed to provide that care, and the utilization and capacity of that resource. By using sophisticated managerial accounting, they discovered several opportunities to improve value:

- Eliminate unnecessary process variations and processes that don’t add value
- Improve resource capacity utilization
- Deliver the right processes at the right location
- Match clinical skills to the process
- Speed up cycle time
- Optimize over the full cycle of care

The remedy to the cost crisis does not require breakthroughs in medical science or new governmental regulation, but rather improved ways to accurately measure costs and compare them with outcomes. Educating and engaging all members of the healthcare team, through process mapping of patient care delivery, has the potential to reduce costs while improving outcomes.

Finance

“Markets are constantly in a state of uncertainty and flux and money is made by discounting the obvious and betting on the unexpected.”

George Soros

The goal of finance (Box 5.3) is to maximize corporate value while minimizing the firm’s financial risks.¹¹ If accounting is the language and grammar of business, then finance is a combination of poetry and theoretical physics, with some rock ‘n’ roll added to keep the mix interesting. The central thesis of finance is that risk can be managed successfully, in such a way that wealth is created, by combining the variables of cash, assets, supply chain, and human capital, to produce a good or service that is more valuable than the cost of production. The consumer, however, is the final arbiter who decides if the good or service is more valuable than the cost of the inputs, and if the output is more valuable than the price the consumer is willing to pay. If so, the consumer exchanges money for the good or service.

Risk can be measured statistically and therefore, given assumptions that are known with certainty, the outcome of decision-making can be predicted with specific probability. Thus, the decision to make an investment in a new piece of equipment, a new employee, a new product line, or to purchase another company, can be made with a certain level of confidence. However, when some variables are

unknown (ambiguity) or when no variables are known (true uncertainty), sound financial management may not be possible, to the point that flipping a coin may provide more insight regarding outcomes.

This section will introduce common tools used by financial managers when analyzing a financial scenario, to determine go/no-go decisions about acquiring and allocating assets. While understanding the mechanics of such calculations is not essential, understanding the logic behind the decision-making is critical, as well as understanding the significance of the results. We will review the following concepts: Time value of money, opportunity cost, net present value (NPV), discounted cash flows (DCF), weighted average cost of capital (WACC) and the hurdle rate, return on investment (ROI), and internal rate of return (IRR).

Time value of money

Money increases in value over time, and such appreciation is actually logarithmic (although it takes a while to get going!). Even Einstein conceded, "The most powerful force in the universe is compound interest." Essentially, a dollar today is worth a slightly more tomorrow and a lot more in ten years. A dollar invested in a money market account with an annual return of 2% will yield 2 pennies next year, increasing the value of this investment to \$1.02, which is future value of today's dollar. The formula for the time value of money is:

$$\text{Present value (PV)} = \text{future value} / (1 + \text{interest rate})^{\# \text{ of periods}}$$

Why does money have a time value? Economists attribute this to two factors: postponement of consumption and expectations of inflation. Interest rates are a hedge against this type of depreciation. As risk of an investment increases, then the reward to the investor needs to increase, to convince the investor to part with one dollar today, in hopes of having possibly \$1.20 next year (which would be a 20% return). The actual rate that money can appreciate is determined by multiple factors, such as the risk of the specific investment, the performance of the stock market, the return on US Treasury bonds, and the monetary policy established by the Federal Reserve, which sets the overnight lending rates to commercial markets.

Consequently, obtaining capital costs money. If one borrows money from the bank, this loan creates risk for that institution, so the bank will need to collect more money from the borrower, when the debt is repaid, at some point in the future. But here is the catch: banks need to charge not only for the time value of money, which is their expected rate of return (also called the discount rate), but the bank must also hedge against your riskiness as a borrower, driving up the cost of capital and increasing the interest rate that you must pay. In fact, if the bank can make a safer investment, with a possibly higher rate of return, then the bank should not pursue the loan.

Opportunity cost

When considering a new project or purchasing a piece of equipment, one should proceed if the intrinsic value of the asset equals or exceeds its cost. What one must also consider, though, is the opportunity cost of tying up precious time,

money, and energy in that project or asset, when those resources could be invested elsewhere. The definition of opportunity cost is the potential benefit forgone from not following the financially optimal course of action. Rather than thinking in yes/no parameters, the investor should make either/or decisions, searching for other opportunities, until he or she can compare the proposed course of action with the next best alternative. In the world of surgery, where most of physician revenue is generated from procedures, any activity that takes the surgeon out of the operating room should be carefully compared to what the surgeon could accomplish by staying in the OR.

Net present value (NPV) and discounted cash flows (DCF)

The decision to pursue a project, when economic considerations are important, involves determining the net present value of that opportunity. NPV is calculated by adding a time-series of cash flows, both incoming and outgoing, that the project is expected to produce, over a series of future periods. This calculation would include the initial cost of purchasing the asset, at DCF_0 , plus the anticipated revenue that the asset would generate, from DCF_1 to DCF_n . Each future cash flow must be discounted back to its present value.

$$NPV_{0-n} = DCF_0 + DCF_1 + DCF_2 + \dots + DCF_n$$

where n = number of periods

If the NPV is >0 , then the investment would add value to the firm, and the project may be accepted. If the NPV is <0 , then the investment would subtract value from the firm, and the project should be rejected. The discount rate selected is often the firm's weighted average cost of capital (WACC), which blends the cost of debt (borrowing money) with the cost of equity (shareholders' expected returns on their stock). Another approach in selecting the appropriate discount rate is to determine the rate that another investment would yield, if this capital were used in a different project. This required rate of return is often referred to as the hurdle rate, which is higher for riskier projects and lower for safer ones. The hurdle rate represents the expected rate of return for risk-free projects (tied to the US Treasury bill) plus the potential rate of return for risky projects.

Return on investment (ROI)

After one has projected future cash flows for an investment, how can one evaluate these future cash flows, in terms of the value of this investment? Several approaches are helpful in deciding the potential value of future ventures and in retrospectively examining the actual value of past ventures. These methodologies include: formal ROI or yield, the payback method, the internal rate of return (IRR), and the NPV/DCF model. The most rigorous and powerful technique is NPV/DCF analysis, but limitations include multiple assumptions regarding future cash flows, selecting the appropriate discount rate, and complexity of the calculation. As a result, predictions using NPV tend to be conservative, but at least they incorporate the time value of money, so that the investor can make decisions based on the value of today's dollars.

A much simpler approach to calculating ROI is yield, which is represented by the following formula:

$$\text{Yield} = (\text{gain from investment} - \text{cost of investment}) / \text{cost of investment}$$

Yield, however, is expressed as a percentage, and therefore gives little information about the magnitude of the value of the investment. Furthermore, yield can be easily manipulated by using varied metrics to define “gain” and “cost.” Yield is helpful when comparing similar products or services, within a market or industry.

The payback method, which measures the time required for the cash flow from the project to pay for the original investment, is also quite popular with mid-level managers, who need to justify the purchase of capital equipment and predict time to break-even.

$$\text{Payback time} = \text{cost of investment} / \text{annual cash flow}$$

What payback period does not take into account is depreciation of the equipment, useful lifespan of the asset, and residual value of the asset at the end of the period. Furthermore, cash flows for a project or asset usually change from year to year, and therefore the payback period only estimates when the project or asset reaches break-even. If the useful life of the investment is greater than the payback time, then the investment should be pursued, at least for financial reasons.

Another technique used to assess ROI is the internal rate of return, or IRR. Instead of assuming a particular discount rate for an investment and calculating the NPV, the IRR method determines the actual return projected by the cash flows. The IRR is then compared with the firm’s hurdle rate,

which may vary for different projects, depending upon the risk, the time horizon for the returns, and the cost of capital for the firm or WACC. Another way of understanding this method is that IRR represents the hurdle rate necessary to make NPV = 0. Problems with using IRR include not quantifying the overall value of the project, as well as how long the company can anticipate the length of the return. Nevertheless, IRR, payback method, and yield are helpful when communicating potential ROI to stakeholders, because of their simplicity and ease of understanding.

Economics

“Economists are about as useful as astrologers in predicting the future (and, like astrologers, they never let failure on one occasion diminish certitude on the next).”

Arthur Schlesinger, Jr.

The sheer enormity of the field of economics prohibits a detailed review in this setting, but nevertheless, key concepts can be outlined. The entire discipline ranges from macroeconomics to microeconomics, from normative economics to behavioral economics, from heterodox economics to game theory (Box 5.4).

Like other branches of economics, healthcare economics deals with decision-making in the setting of uncertainty, limited resources, and variable demand.^{12–15} However, healthcare economics is distinctly different from other branches of economics, because healthcare is an industry that includes extensive government intervention and regulation; asymmetry of information between provider, patient, and payer; lack of precise metrics, with regard to patient outcomes; and considerable externalities, which are the downstream effects on other entities, outside of the healthcare system.

Demand for a good or service is based upon a buyer’s willingness to pay, which in turn is influenced by the buyer’s tastes or needs, the consumer’s income or wealth, and the availability of substitute and complementary goods. Demand curves can then be constructed to describe an individual’s or a population’s willingness to purchase: as price increases, demand decreases. Price elasticity represents the change in quantity demanded as a function in change of price and is crucial to the way that markets adjust. Mathematically, this relationship can be expressed as:

$$E_d = \text{delta } Q / \text{delta } P$$

where E_d is the coefficient for the price elasticity of demand

(Although E_d is almost always negative, economists typically use the absolute value of E_d , making this a positive number)

Q = quantity of good or service

P = price of good or service

Elasticity coefficients can be interpreted as follows:

$E_d = 0$ perfectly inelastic demand

$-1 < E_d < 0$ relatively inelastic demand

$E_d = -1$ unitary elasticity

$E_d < -1$ elastic demand

$E_d = -1/0$ perfectly elastic demand

BOX 5.3 Idea watch: finance

Reference: McGrath RG. Transient advantage: strategy for turbulent times. *Harvard Business Review*. 2013;91:62–70.⁶⁷

Given the volatility of the economic markets over most of the 21st century, the previous dogma that strategy consists of establishing a unique competitive position, sustained for long periods of time, may no longer be relevant for many businesses. In the age of information, **transient advantage** may be the new normal. Businesses must learn to launch new strategic initiatives, again and again, based on a new set of operational capabilities. Just like a diversified portfolio of assets may hedge against risk, a portfolio of advantages that can be quickly built, and quickly abandoned, may improve the financial position of the company, by maintaining multiple revenue streams that result in combined net positive cash flows.

McGrath warns that businesses operating in a high-velocity setting will need to avoid traps previously viewed as advantages: first-mover, total quality management, white space positioning, and incremental innovation. Instead, companies should consider the following shifts:

- Think about arenas, not industries
- Set broad themes, and then let people experiment
- Adopt metrics that support entrepreneurial growth
- Focus on experiences and solutions to problems
- Build strong relationships and networks
- Avoid brutal restructuring; learn healthy disengagement
- Get systematic about early stage innovation
- Experiment, iterate, learn.

Goods or services with close substitutes, such as Botox® and Dysport®, have a flat, elastic curve, in which small changes in price produce large changes in demand. Other goods and services may have steep, inelastic demand curves, in which large changes in price may have minimal effects on demand; this is the case for necessities with few substitutes, some luxury items, and products with intense brand loyalty. Price elasticity for a given good or service may also vary, based upon the specific segment of the market targeted, and may be influenced by macroeconomic forces. When the purchaser does not directly pay for the good consumed or the service provided, such as a patient whose surgery is paid for by third-party insurance, price elasticity is likely to be relatively inelastic. Adding a copay or deductible transfers some of the cost to the consumer and increases the elasticity of demand for healthcare.

Supply of a good or service depends on a firm's short-term and long-run strategic goals. Decisions about supply are based initially on marginal costs, which vary with level of production. As production increases, so do marginal costs. However, average fixed costs decrease with increasing volume. These curves are combined to produce a U-shaped curve of average total cost, the nadir of which is the lowest price that the firm can charge and break even. A company can offer a good or service, as long as the market price remains above the average total costs. An aggregate market supply curve demonstrates that as price increases, more firms are willing and able to produce outputs.

Market equilibrium occurs when the supply and demand forces adjust to a price and quantity that satisfy both producers and consumers. Markets will move in predictable ways, based upon changes in supply and demand. Increased supply causes the equilibrium price to fall and the equilibrium quantity to increase. Conversely, new demand for a product or service will cause the equilibrium price to rise, with a subsequent increase in the equilibrium quantity.

Real markets, however, are messy and may behave in ways that only approach these rules. For these economic models to work, markets must have perfect competition, in which products are identical, sellers and buyers do not engage in strategic manipulation of supply and demand, players make rational choices, entry and exit barriers are non-existent, and participants are fully informed. Such a market does not exist. Predicting how economic forces shape the healthcare market is a considerable challenge, given that such competition is far from perfect.

Firms can gain strategic advantage, then, by exploiting the inefficiencies of the market. Ethical approaches include product differentiation, segmentation of the market, responding to new cultural, social, and political shifts, and using technology and innovation to create new value propositions. Unethical tactics would involve maintaining an asymmetry of information between consumer and producer, taking advantage of irrational decision-making, artificially creating demand or limiting supply, collusion with other players, and creating impassable barriers of entry for new participants. In the healthcare industry, providers must remain cognizant of these opportunities – both ethical and unethical – and maintain a level of responsibility that ensures professionalism at all times.

In summary, markets strive for equilibrium, but adjustments in supply and demand may not lead to productive efficiency, which by itself is not a guarantee of the fair

BOX 5.4 Idea watch: economics

Reference: Kaplan RS, Porter ME. Motivating salespeople: what really works. *Harvard Business Review*. 2011;90:71–75.⁶⁸

How do we improve the productivity of our employees? In healthcare, providers are expected to see more patients, improve quality of care, and optimize patient satisfaction, often with reduced resources. Fundamentally, incentivizing physicians, nurses, and therapists is a microeconomic problem, in which incentives should be aligned with performance to influence behavior. Laggards, Core Performers, and Stars each respond to different rewards, and therefore compensation plans should be structured differently to induce a higher level of productivity. Companies that structure their incentive plans based on these differences will realize better results across the performance curve:

Motivating Laggards

- Recognize, first, that this group is heterogeneous and can include new hires, complacent senior providers, and people who are just less talented than their colleagues; one size does not fit all
- Introduce more frequent, pace-setting bonuses
- Create natural, cultural, and program-specific social pressures

Motivating Core Performers

- Establish multi-tier targets for productivity
- Have sales or performance contests with awards that vary in nature and value

Motivating Stars

- Avoid ceilings on pay; controlling costs also encourages the stars to quit working
- Develop super-achievement commission rates.

distribution of wealth in society. A final quandary to ponder: not all of the costs and benefits of a transaction accrue to the buyer and the seller. These externalities – downstream effects on society – may be beneficial (new technology that extends life), but are too often detrimental (production of medical waste products). How can we incorporate these externalities into our decision-making, so that we increase the total social value of our actions?

Marketing

“Good companies will meet needs; great companies will create markets.”

Philip Kotler

Business could not exist without the customer, and marketing is the process that enables business to connect with the customer (Box 5.5).^{16,17} Marketing strategy identifies, attracts, satisfies, and retains customers. Seeking to build more than a single exchange between the producer and the consumer (or in healthcare, the provider and the patient), marketing is first and foremost driven by customer needs and desires. The ideal approach in marketing is initially to understand the customers in the context of their environment, which includes not only assessment of market size but also competitive forces, barriers to entry, and market structure. Next, marketing seeks to develop a specific product or service offering, based upon

anticipated customer needs that may or may not be adequately met, or may not even be appreciated. Finally, marketing strives to deliver customer value, in the form of price point, quality, and distribution.

Although marketing strategy has been often oversimplified by focusing on the “4Ps” – **product, price, promotion, place-ment** – this is a good starting point for our review. Product refers to the characteristics and defining features of a good or service. Price is determined by factoring in cost of production with what additional value can be extracted by the producer, based upon value-added features and the demand for the good or service. Calculating break-even volume is important to determine if a pricing strategy is reasonable. The formula for finding out how many units a company must sell, so that its costs are covered, is represented as follows:

$$\text{Break-even unit volume} = \frac{\text{fixed costs/}}{(\text{sales price} - \text{variable costs})}$$

To achieve a specific profit target, the formula can be modified as follows:

$$\text{Volume} = \frac{(\text{fixed costs} + \text{total profit})/}{(\text{sales price} - \text{variable costs})}$$

Promotion involves the channels that will be necessary through which the company can communicate its message and may involve advertising, use of a sales force, or incentives (bundled pricing, discounts, rewards, and frequent buyer benefits, for example). Placement is arguably the most important of these variables; marketing experts segment a general market to determine what types of people (young vs old, male vs female, high income vs low income) desire what types of products. Segmentation allows for better allocation of a company's finite resources, enables the firm to target specific high-yield groups, and improves positioning of the product for higher market penetration. In fact, a company can offer related but slightly different products if marketing research demonstrates that multiple segments have slightly different needs. Instead of pursuing a one-size-fits-all philosophy and missing segments of the market, a firm can employ marketing analysis to justify, with confidence, multiple offerings of related products.

Over the past two decades, in which consumers have been empowered by the internet (online auctions, availability of product reviews, and easy comparison of prices), marketing has shifted from a supply-side model to a demand-based one, in which customers' perspectives are factored into the supplier-centric approach of the 4Ps. Products are now viewed as solutions for the customer, promotion now includes transfer of information, price has been replaced by consumer value, and placement is viewed as access.

To identify market segments that might purchase a product or service, and to determine what qualities that segment would find most valuable, marketing research utilizes complex analytical tools such as regression analysis, conjoint analysis, perceptual maps, and scenario planning to make decisions. Fig. 5.2 demonstrates the crowded landscape of facial rejuvenation, in which patients may choose from a number of interventions, based upon such parameters as price, durability, invasiveness, and time to recovery. Marketing seeks to identify which customers want what procedures and to target that group specifically. Occasionally, uncontested market

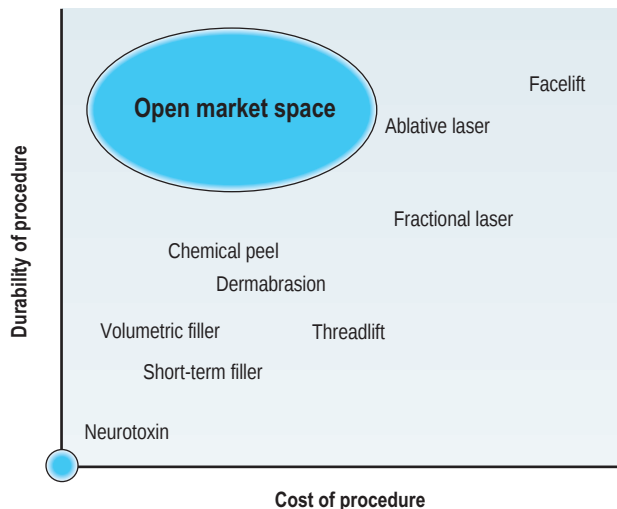


Fig. 5.2 Marketing: perceptual map of facial rejuvenation.

space is discovered, based upon changing customer preferences, or opens up, due to advances in technology.

The act of connecting customer to product or service is central to the charge of marketing and can reap tremendous returns, in terms of revenue, branding, and goodwill. As such, marketing is viewed as an investment by the company, similar to research and development, in which return on investment is predicted and carefully studied, along with other metrics such as market share, customer attrition, customer satisfaction, exchanges and returns, and size of accounts receivable. Other research tools include customer focus groups, demographic data, and customer questionnaires.

In addition to using such strategies as segmentation, targeting, and positioning, marketing also can utilize branding as a powerful tool to communicate the qualities of a new offering. In many ways, a strong brand serves, albeit not legally, as a promise that the new product or service will be similar to previous offerings. Branding can include a logo, phrase, image, or feeling that serves as a placeholder for the company and its reputation.

One strategy that is not particularly effective but must be mentioned, to warn against, is that of perceptual shifting. This occurs when: 1) promotion attempts to shift the needs and desires of a targeted group, so that they believe that they need or desire the product or service; or when 2) promotion shifts the perceived qualities of the offering, so that these features more closely correspond with the needs and desires of the targeted group. Such a strategy will produce a very short-term effect, which may temporarily improve sales, but will have disastrous long-term effects on the relationship with the customer. This strategy is employed when firms do not desire repeat transactions with their customer or when a product is reaching obsolescence and the entire industry is shrinking.

With the recent decline in print media and other traditional communication outlets such as radio and network TV, marketing has turned to the internet to promote goods and services, provide information to the consumer, and match the appropriate offering with the correct group. Many economists arguably contend that in our new digital age, the cost of storing information is approaching zero and the value of

BOX 5.5 Idea watch: marketing

Reference: Avery J, Fournier S, Wittenbraker J. Unlock the mysteries of your customer relationships. *Harvard Business Review*. 2014;92:72–81.⁶⁹

Many consumer companies, including service industries like healthcare, lack relational intelligence and do not appreciate the different kinds of relationships that their customers have with their brand, their product, and their service. Each type of customer relationship is based on that customer's experience, expectations, and future desires.

Customers can now be described as strangers, flings, acquaintances, buddies, teammates, best friends, and even enemies. As such, marketing divisions must crunch big data to determine the signal within the noise, in terms of providing the right customer with the right product or service within the context of the right experience. Meeting or exceeding consumers' needs must still occur, but marketing experts must consider the new rules, which include:

- Bolster desired relationships
- Renegotiate existing relationships
- Reorganize marketing strategy around relationships
- Create new roles for employees to develop relationships
- Expand the marketing umbrella within the organization create a culture of relationship-driven strategy

information may creep toward infinity.⁶³ Despite whether or not this can be proven, it is clear that digital information has completely changed the rules of marketing. Companies can gather specific information about consumers, based upon their shopping habits at Amazon, their friends on Facebook, what they write on blogs in the Huffington post, and what articles they read at CNN.com. For a fraction of the cost of traditional media, firms can reach out to their customers through direct email or via search engines. Marketing departments now focus on search engine optimization and search engine marketing. As some companies experiment with new revenue streams, both online and offline, some products may be offered for free, while related services may cost a premium.

Operations

"Any customer can have a car painted any color that he wants, so long as it is black."

Henry Ford

Operations can be defined as matching supply with demand (Box 5.6).^{18,19} Although economists can describe how prices change with alterations in supply and demand, managers responsible for production of inventory or for coordination of services have an entirely different perspective: excess demand is lost revenue, and excess supply is wasted resources. How the manager balances supply and demand determines not only potential revenue from goods and services but also operating costs, which together yield operating income for the firm.

Operational effectiveness is critical to the firm's success; in fact, this can be a source of competitive advantage. Companies that get more from their inputs, or use fewer inputs, to produce higher quality outputs will be able to offer goods or services

at lower costs than their competitors or extract more financial value from these goods and services. This flow of inputs to outputs is also called the supply chain, and when managed well, adds value to the final product, before this is passed on to the consumer.

To optimize the flow of this value chain, the field of operations utilizes elements of queueing theory to predict and control demand, as well as the theory of constraints, to predict and control supply. Perhaps the greatest challenge in determining demand for a good or service is variability. In medicine, for example, long clinic waits to see a physician are often due to variability in patient arrival times, which is compounded by a variability in service times by the provider. This is why patients of a certain type are often scheduled in batches, to minimize the variability on both sides of the equation. In the service industry, key metrics that should be tracked, in an effort to improve operational effectiveness, include:

Capacity = maximum supply a process can generate

Capacity utilization = arrival rate/service rate

Throughput time = wait time + service time

Flow time = (1/service rate)/(1 – capacity utilization)

Inventory = average flow rate ×
average flow time (Little's Law)

Inventory turns = 1/flow time = COGS/inventory

Bottlenecks in the production process (for goods) or delivery process (for services) occur when the demand at a specific station in the flow process is greater than the outputs produced at that station. At any given point, a process has technically only one bottleneck, which is defined as the resource with the lowest capacity. Flow through a station can be measured to identify the bottleneck, but this point of constraint is often evident by high utilization, no slack or buffer, piled-up inventory, and complaints from workers and consumers.

Principles used to match supply with demand include:

1. Since the limiting resource defines capacity, focus on improving output at the bottleneck (this, of course, creates a new bottleneck somewhere else in the system).
2. Maintain enough inventory and work-in-process to keep the pipeline flowing, to prevent stock-out, and to anticipate variability in demand, but not too much that capital is over-invested on unfinished goods or unused services.
3. Systems or stations operating at close to 100% capacity are not sustainable; 80% utilization is considered to be a reasonable target.
4. Plan carefully, as variability and uncertainty can propagate along the supply chain, creating a bull-whip effect of increasing impact that yields far too much or far too little output.
5. Prevention costs less than inspection and correction; never add value to a part that is defective.
6. Never allow the cause of the problem to persist by working around it.
7. High quality is not free, but it can be a great investment.

8. Forecasts are always wrong, sometimes more so than others.
9. Service industries face unique challenges that involve customization of the output and high degree of labor interaction.

In an effort to improve operational efficiency, a number of methods have been developed to reduce defects, increase throughput, and improve quality. Lean manufacturing is a production process in which any expenditure or resource that does not add value to the customer is a target for elimination. Originally developed by Toyota, lean manufacturing attempts to “work smarter, not harder” by reducing or eliminating seven sources of waste: overproduction, unnecessary transportation, inventory, motion, defects, over-processing, and waiting. Although this approach yields only incremental improvements in operations, the system itself was an innovation that provided competitive advantage over other firms in the automobile production industry.

Another methodology that provides incremental improvements, through reduction in defects and quality improvement, is Six Sigma, originally developed by Motorola. Using the DMAIC model of **Define, Measure, Analyze, Improve, and Control**, experts (known as Black Belts, Green Belts, and Yellow Belts, depending upon level of training and responsibility) attempt to improve the quality of process outputs by minimizing variability in the production line and reducing defects or errors to less than 3 per million (6 standard deviations from the desired target, thus 6-sigma). Quality management tools used to identify areas needing improvement include business process mapping, cost-benefit analysis, critical to quality trees, Pareto charts, and SIPOC analysis (suppliers, inputs, process, outputs, and customers). After determining the root cause of defects or inefficiencies, Six Sigma experts apply and test such interventions as contingency planning, parallel processing, and workflow redesign to reduce defects, improve quality, and maximize throughput. Although the methodology of Six Sigma provides only incremental improvement to inefficient systems and may, in fact, stifle “outside-of-the-box” innovation, improvements in operational productivity and quality may yield substantial financial rewards, in terms of cost savings, company goodwill and branding, and customer and employee satisfaction.

In service industries, the value chain can be strengthened by not only focusing on quality but also stakeholder happiness. In “Putting the service-profit chain to work”, Heskett *et al.* describe a model of stakeholder satisfaction, in which internal service quality yields employee retention and productivity, which in turn drives up external service value, securing customer loyalty and retention, which has direct impact on revenue growth and profitability.²⁰ Employees and consumers can move from a zone of indifference to zones of affection or defection, depending upon their level of satisfaction. In fact, Jones and Sasser argue, in “Why satisfied customers defect,” that complete customer satisfaction is the key to securing loyalty – intent to repurchase – and generate superior long-term financial performance.²¹ Different industries have different loyalty/satisfaction curves, creating a mixture of consumers that includes apostles, loyalists, mercenaries, defectors, hostages, and terrorists. Companies should direct efforts at achieving complete satisfaction to retain the loyalists and attract the mercenaries (the apostles will stay), while the

BOX 5.6 Idea watch: service operations

Reference: Porter ME, Lee TH. The strategy that will fix health care. *Harvard Business Review*. 2013;91:50–70.⁷⁰

Perhaps the industry with the most potential, and most need, to improve its performance is healthcare. The combination of rising costs, uneven quality, limited access, and disparate outcomes has led to a crisis in which the health of our economy, and our nation, is at stake. Michael Porter is calling for a fundamentally new strategy. Previous efforts, such as changing public policy, improving patient safety, implementing evidence-based guidelines, involving patients as consumers, reducing fraud, and implementing electronic health records, have yielded small, incremental changes, at best. Instead, value must become the overarching goal.

Transformation to a high-value healthcare delivery system must involve the simultaneous cooperation of administrators, providers, patients, health plans, and employers, to deploy the following strategic agenda:

- Organize into integrated practice units
- Measure outcomes and costs for every patient
- Develop bundled prices for care cycles
- Integrate care delivery systems
- Expand areas of excellence across geography
- Build and exploit an enabling information technology platform

terrorists should not be pursued and hostages should be let go. In healthcare, patients who are not completely satisfied or mostly satisfied will find other providers.

Innovation

“Companies that enjoy enduring success have core values and a core purpose that remain fixed, while their business strategies and practices endlessly adapt to a changing world.”

James Collins and Jerry Porras

Whereas the field of operations provides value through incremental improvement, innovation (Box 5.7) produces radical or revolutionary changes in thinking, design, products, processes, and even organizations.^{22–25} Operations serve to exploit existing inefficiencies, with the goal of lower costs, faster production, and higher quality, via such interventions as tighter supply chain coordination, lean manufacturing techniques, and zero-defect policies. Innovation, on the other hand, disrupts the current paradigm and not only expands the existing market but may create entirely new markets. Thomas Krummel, a pediatric surgeon who directs the Stanford Biodesign Program, describes a sequence of discovery, invention, innovation, and entrepreneurship that is the blueprint for translational medicine.²⁴ More importantly, he asks, “why should innovation be left to chance?” and provides a cogent argument for studying, understanding, and teaching innovation. Medical knowledge can be utilized directly in patient care, but training other physicians, developing new solutions, and applying new technologies can increase the impact of surgeons exponentially.

A reasonable question, which has a surprising answer, is “why do we need to innovate?” Peter Drucker, in fact, wrote that the two essential functions of a company are innovation

and marketing, because these create real value; all other processes are costs.²² Since the business environment is always changing, the position of a company, relative to its competition, new entrants, substitutes, suppliers, and consumers, is also in flux. A company that enjoys dominant market share today could become easily displaced tomorrow. Apart from innovation, the only competitive advantage that a company can maintain is based upon incremental improvements in price, quality, and access – until a new company introduces an innovation that dramatically affects these qualities, significantly expands the size of the market, or actually changes customer needs and preferences. Innovation is most effective and needed during periods of stability, whereas process improvement is most valuable to a company during periods of growth.

Successful innovation requires discipline and hard work, in addition to creativity. Companies that have mastered the process of innovation, such as Apple, Mayo Clinic, and the design firm Ideo, follow a roadmap that consists of four phases: breakthrough or discovery, platform development, derivative changes, and maintenance. Through a carefully orchestrated plan, in which these phases overlap, project managers allocate resources (time, money, people) based upon importance of each phase, level of uncertainty, and location in the critical pathway. Apple may introduce a new product, such as the iPod, iPhone, and iPad every few years, but each of these devices undergoes an iterative process of

improvement and value-added upgrades in technology. By having a diverse portfolio of new products, Apple is ensuring the success of its company, similar to a mutual fund with multiple investments. Occasionally, such innovation is disruptive, displacing some products, increasing competition with a company's own products, and creating new markets for other entrants. Such is the case with digital music; Apple changed from a computer company to an information and communications company, within a decade. Apple was able to apply breakthrough technology to create new products. If Apple had focused on incremental improvements in their operating system or software, as Microsoft has done, then such spinoff applications as e-books, online newspapers, and of course iTunes might not yet exist. The real challenge will come from Google, which started as a search engine but now intends to dominate the landscape of cloud computing.

Three drivers of successful innovation are understanding the consumer, “crossing the chasm”, and managing failure. To succeed over a long-term horizon, companies need to serve and retain their existing customers and acquire new ones by applying incremental and disruptive technologies. The focus of any commercial venture should start with the voice of the customer – listening to what the customer wants – and should finish with what the customer needs. Good marketing may be able to identify needs that do not yet exist, or segments of the population that have not been identified. Second, anticipate who will need the product or service, and when. Prototypes and early versions (think iPhone v1.0) are critical in attracting the innovators (our medical students) and early adopters (our residents), who will demonstrate product viability and create an early buzz. Return on investment, however, will not occur until the early majority (me) and late majority (my boss) adopts this technology. Even laggards, who usually resist new technology, may be an attractive group to target, as they may become the early adopters of the next technology. Crossing this chasm, from early adoption to market penetration, is where most companies fail. The third component of successful innovation, then, is learning from failure and managing failure. Just as lean manufacturing and Six Sigma permit

BOX 5.7 Idea watch: innovation

Reference: Christensen CM, Raynor M, McDonald R. One more time: what is disruptive innovation? *Harvard Business Review*. 2015;93:44–53.⁷¹

Two decades after introducing the theory of “disruptive innovation”, Clayton Christensen and colleagues set the record straight. While disruptive innovation has proven to be a powerful way to fuel innovation-driven growth, not all innovation is disruptive, and certainly not all disruption is innovative.

The authors remind us, “disruption describes a process whereby a smaller company with fewer resources is able to successfully challenge established incumbent businesses . . . which focus on improving their products and services for their most demanding (and usually most profitable) customers” – exceeding the needs of some segments and ignoring the needs of others. Uber, for example, is clearly transforming the taxi business, but its financial and strategic achievements do not qualify the company as disruptive. According to Christensen's theory:

- Disruptive innovations originate in low-end or new-market footholds
- Disruptive innovations don't catch on with mainstream customers until quality catches up with their standards.

Although Uber has increased total demand in the taxi sector – because the company developed a better, less expensive solution to a widespread customer need – Uber did not start in low-end or unserved markets. Instead, Uber created sustaining innovations that actually improve the taxi business, such as booking rides on a smartphone app, using GPS to reduce wait times, offering cashless payments, and providing passengers and drivers with the ability to rate each other. Furthermore, Uber uses a variable pricing algorithm that usually results in a less expensive ride, which is more punctual and reliable than traditional taxi services. An area where Uber may truly produce a disruptive innovation is the application of this technology to ride-sharing and car-pooling, as an alternative to our solo commutes to work.

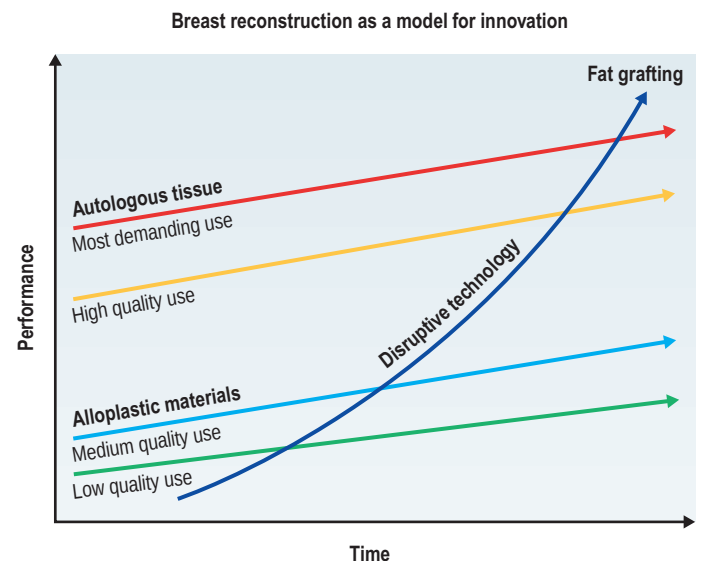


Fig. 5.3 Innovation: incremental change in breast reconstruction.

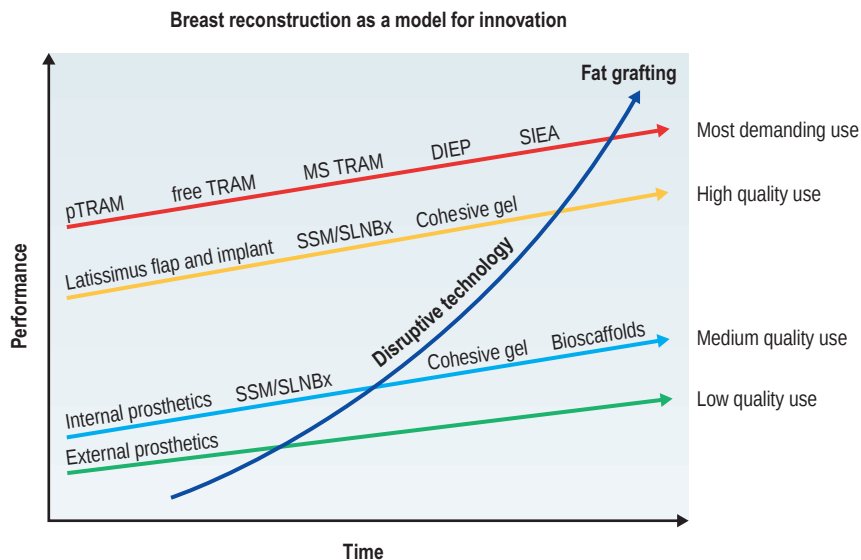


Fig. 5.4 Innovation: disruptive change in breast reconstruction.

incremental improvement in production systems, controlled experimentation increases the yield of innovation efforts. Measures to minimize risk include separation of invention from execution, maintaining a diverse and deep pipeline of ideas and projects, and collaborating with people outside of your area of technical expertise or “comfort zone”.

In the field of plastic surgery, breast reconstruction has experienced both incremental and disruptive innovation, involving alloplastic materials that continue to be refined (silicone and saline implants), as well as surgical methods that utilize vascularized tissue (latissimus, transverse rectus abdominis myocutaneous (TRAM), and perforator flaps). The recent introduction of fat grafting, initially used to correct contour deformities, may actually supersede conventional methods of reconstruction, to become a primary method of breast replacement (Figs 5.3 & 5.4). In addition to such factors as durability and cost of reconstruction, the value chain will also need to incorporate patient and provider preferences, until a new market equilibrium is established.

to gain the support of investment bankers, suppliers, and customers.

Perhaps the most important resource to an entrepreneur, though, is an asymmetry of knowledge. Entrepreneurs may be aware of: 1) macro-economic forces yielding change in demographic, social, and cultural norms; 2) new technologies without defined applications; and 3) existing inefficiencies embedded within current industries. Such incongruities, in the setting of new technology and changing markets, represent tempting opportunities for entrepreneurs. Good entrepreneurs find opportunities; great entrepreneurs make opportunities. One example of capturing latent value in healthcare is to move ambulatory services out of the hospital, which carries a high overhead burden, and into ambulatory settings, where overhead costs are lower, and variable direct costs can be more accurately measured and controlled. An accredited, office-based surgery facility may actually improve quality and safety, in addition to decreasing the cost of care and improving patient satisfaction (Figs 5.5 & 5.6). Moving

Entrepreneurship

“The people who get on in this world are the people who get up and look for the circumstances they want, and, if they can’t find them, make them.”

George Bernard Shaw

Whereas technology is the way that you do things and innovation is the way you do new things, entrepreneurship (Box 5.8) is the way that you increase the value of what you do.²⁶ Entrepreneurship is a way of thinking, as well as a process, that increases the impact of innovation. An entrepreneur articulates a vision and develops a system that assembles inputs, creates a product, service, or information, and captures new value from the outputs. Entrepreneurial leaders act to bring a future business possibility into existence, with a sense of urgency, not constrained by limitations in capital, personnel, or productions. Instead, the entrepreneur utilizes his or her imagination, drive, passion, and networking,

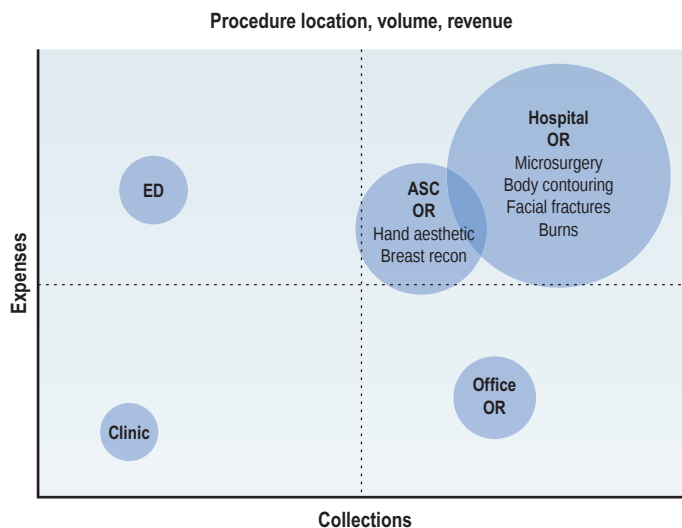


Fig. 5.5 Entrepreneurship: location of services, volume, and revenue. ASC, ambulatory surgical center; ED, emergency department; OR, operating room.

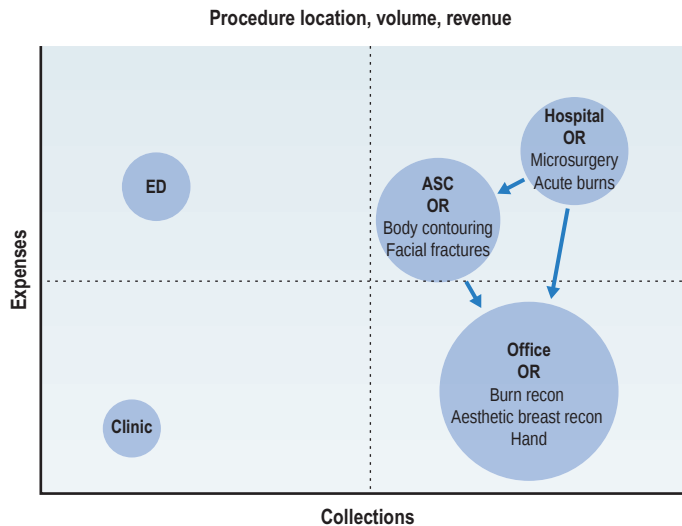


Fig. 5.6 Entrepreneurship: effect of shifting location of care. ASC, ambulatory surgical center; ED, emergency department; OR, operating room.

the correct activities to the most appropriate location makes sense, creates value, and improves the patient-provider experience.

What is the process, then, for turning a challenge into an opportunity? The first and single most important act is to establish a value proposition, which can be defined as that core competency which makes your product or service unique and valuable. The value proposition presents a problem and solution, describes what you do and how you do it, and serves to differentiate you from the competition – all in one sentence. From this value proposition, the entrepreneur next develops a business model, which must then be translated into a business plan. The addition of a marketing plan, financial pro formas, and an operations template helps the entrepreneur create a true value-chain, mapping out the process path of the product or service (Fig. 5.7). These elements are linked by strategy, which describes how to achieve the value proposition, or specifically, how the product or service will reach the initial beachhead segment and possibly penetrate the general market (Fig. 5.8). Leadership serves as the cohesive force that manages, directs, and grows the entire enterprise. Leaders must fulfill the value proposition and ensure that the mission, vision, and values of the enterprise remain consistent and virtuous.

With details carefully thought out and available to potential stakeholders, the entrepreneur must seek support for this plan

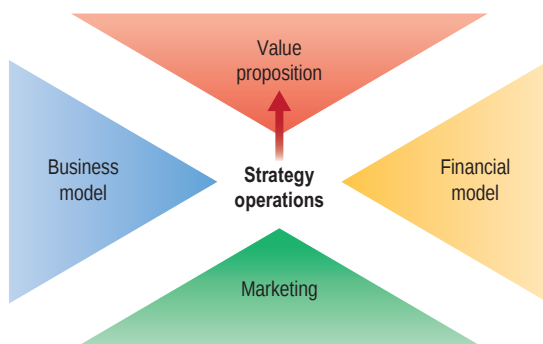


Fig. 5.7 Entrepreneurship: aligning the elements of a new venture.

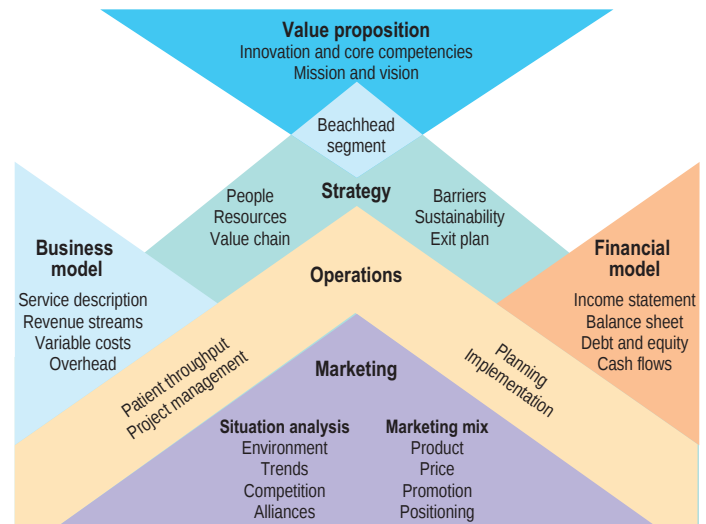


Fig. 5.8 Entrepreneurship: linking the elements of a new venture.

through different types of communication. The elevator pitch, which is a 30-second distillation of the new venture, is designed to attract interest and pique the listener's curiosity. The executive summary is a one-page summary of the business plan, whereas the business plan is a highly detailed document, ranging from 20 to 60 pages, designed to address specific questions, as investors look further into the venture. A ten-minute overview, typically delivered as a PowerPoint talk, is also necessary to get investors to actually read the business plan.

At every stage, the entrepreneur seeks to increase the interest of potential stakeholders and actively listens to feedback, so that the business plan can be revised, rewritten, and refocused, as often as needed. If the entrepreneur can gain the commitment of the stakeholders, then begins the process of raising capital, carefully managing cash, and coordinating logistics. Entrepreneurs typically bootstrap for as long as they can, utilizing human, intellectual, and social capital, rather than borrowing money or seeking outside funding. Entrepreneurs know that that worst time to raise money is when they absolutely need it, because they must cede control and ownership of the company, each time investors are brought on board with an influx of capital. Venture capital is particularly challenging to accept, because these investment bankers demand a 5–7× return on their investment, within a time horizon of several years, and because their exit strategy is ultimately about sale of the company, not necessarily growth of the company. Angel investors, friends and family, philanthropy and endowments, academic and community grants, small business loans, and even credit cards are more attractive (but limited) sources of capital, permitting the entrepreneur to retain control as long as possible. Finally, the cost of capital is highest at the beginning of the venture, because the risk is greatest, and borrowing costs decrease as the venture becomes more successful.

Writing a business plan is an art that entrepreneurs must master. Fig. 5.7 depicts a model that can be used when designing the elements of a new venture. Much like writing abstracts and journal articles, repetition improves the quality of the product. But unlike scientific papers, which are published

once and do not change, business plans are living documents that are constantly in flux and mandate frequent update. Nevertheless, a typical business plan follows an established model and contains the following components:

1. Executive summary
2. Value proposition
3. Vision, mission, values statement
4. Marketing analysis
 - a. Situation analysis
 - i. Environment
 - ii. Trends
 - iii. Company analysis
 - iv. Competition
 - v. Alliances
 - b. Target market and segmentation
 - c. Positioning and differentiation
 - d. Channels
 - e. Branding
 - f. Sales tools
 - g. Marketing budget
5. Business model
 - a. Description of service or product
 - b. Revenue streams
 - c. Variable costs
 - d. Overhead and fixed costs
6. Strategy
 - a. Beachhead segment
 - b. Value chain
 - c. Growth
 - d. Response to competitors, new entrants, substitutes
7. Governance and management teams
8. Financial pro formas (typically 3–5 years)
 - a. Income statement
 - b. Balance sheet
 - c. Cash flows: operations, financing, investments
 - d. Time to break-even
9. Debt and equity structures
10. Operations
 - a. Planning: Gantt chart
 - b. Implementation
 - c. Throughput assessment
 - d. Continuous improvement plans
11. Legal and regulatory issues
12. Sustainability practices (triple bottom line of people, planet, profit)
13. Barriers and roadblocks
14. Contingency plans
15. Exit strategy

Eventually, the CEO entrepreneur, having built a successful company, must make some major decisions, beyond resource allocation and management of revenue streams. In the short run, the leader will need to delegate operational decisions, while he or she focuses on setting strategy, team building, establishing culture, and reinforcing vision and values. Ultimately, however, the entrepreneur may recognize an internal calling to cede control, so that he or she can begin the process again, with a new idea, perhaps in a new industry, with a new

BOX 5.8 Idea watch: entrepreneurship

Reference: Isaacson W. The real leadership lessons of Steve Jobs. *Harvard Business Review*. 2012;90:92–102.⁷²

Walter Isaacson, former CEO of CNN and author of best-selling biographies on Benjamin Franklin and Albert Einstein, and Steve Jobs, identifies the practices every CEO can try to emulate. Isaacson writes of Jobs: “His saga is the entrepreneurial creation myth writ large.” By transforming seven industries (personal computing, animated films, music, phones, tablet computing, retail stores, and digital publishing), Steve Jobs will be remembered not for his personality, but how he applied imagination to technology and business. Jobs succeeded by pursuing the following practices:

- Focus
 - Simplify
 - Take responsibility end to end
 - When behind, leapfrog
 - Put products before profits
 - Don't be a slave to focus groups
 - Bend reality
 - Impute
 - Push for perfection
 - Tolerate only “A” players
 - Engage face-to-face
 - Know both the big picture and the details
 - Combine humanities with the sciences
 - Stay hungry, stay foolish
- I would add, “Think different.”

market. Others, however, remain with the company as a technical advisor or may serve on the Board of Directors, content with knowing that despite great odds, they created something of value. To paraphrase Steve Jobs, they “put a ding in the universe”.

Sustainable enterprise

“If you want to go fast, go alone. If you want to go far, bring others with you.”

African proverb

Sustainable enterprise (Box 5.9) is a well-established concept that has recently caught the attention of academics in organizational behavior, business executives, supply chain managers, shareholders, and even consumers.^{27–34} The importance of sustainable enterprise is so great that specific companies, as well as entire industries, are reassessing their vision and values, so that organizations can meet a new triple bottom line of “people, planet, and profit.” Green business, or sustainable enterprise, produces no or little negative impact on global or local environments, the community, society, or the economy, with specific attention to progressive human rights and environmental policies.

Previous efforts toward “reduce, reuse, recycle, repair, and redistribute” have been replaced by more aggressive attempts to minimize the carbon footprint of a business, search for renewable energy sources, and lessen the impact of waste materials on the environment, with the goal of establishing a

business that meets the needs of the present, without compromising the ability to meet the needs of the future. Specific examples of sustainable business practices include telecommuting, having a paperless office, minimizing shipping and packing material, leasing equipment that can be returned and refurbished, lean production methods which utilize less raw materials and produce less inventory, continuous improvement processes in the supply chain, and conducting business in LEED-certified buildings, which have lower energy requirements and are made of post-consumer materials. Products of service are durable goods that the manufacturer plans to re-process (thus the term “cradle-to-cradle” when describing the responsibility of the manufacturer), and products of consumption are short-lived materials that are non-toxic and biodegradable.

These sustainable business practices have coalesced into the more formal principle of corporate social responsibility, in which self-regulation is integrated into the overall business model of a company or industry. Businesses have discovered that sustainable practices can generate lasting value to shareholders and stakeholders, in terms of quality, access, and cost of services and goods. Such leaders as Ikea, Nike, Ford, and even Wal-Mart have been able to reduce expenses, minimize risk, increase revenues, and create stronger brands by building environmental and social thinking into their business strategies. Most large companies now have a Chief Sustainability Officer and publish an Annual Sustainability Report that corresponds to the Annual Financial Report.

What can we do in healthcare, and specifically plastic surgery, to leverage green practices and improve our triple bottom line? Interestingly, plastic surgery has been a leader in social justice for decades. Mission trips to developing nations, in which specialized services are provided and re-usable equipment is donated, has been a focus of many plastic surgeons, who could have spent more time in their private practices and generated more money for their businesses. What is especially admirable, in terms of sustainability, is the effort to teach these surgical techniques to providers in developing nations, so that infrastructure is developed and continuity of care is established, between visiting groups and the local communities. For surgeons who do not travel outside of the United States, multiple opportunities exist within our borders to establish similar exchanges, which can include work done at Native American reservations, in underserved areas like Appalachia, or at a community clinic. Even maintaining on-call emergency department privileges, performing lower-reimbursing reconstructive surgery, and assuming some indigent care all count as sustainable efforts, as the surgeon is contributing to a triple bottom line that does not neglect the needs of his or her local community. Such volunteerism is sustainable enterprise and should be a goal for all who practice this craft.

Healthcare, in general, has lagged behind other industries, in terms of sustainable business practices. One definition for sustainable medicine is the improvement of health within the natural life cycle, which seeks to avoid strain on social, environmental, and economic systems, so that new technologies can benefit all people within a community, not just those who can afford it. Extending this definition to the entire population of our planet, we have a moral obligation to provide basic healthcare to all, in the form of clean water, food, vaccinations, and preventive medicine. Jeffrey Sachs, a

BOX 5.9 Idea watch: sustainable enterprise

Reference: Porter ME, Kramer MR. Creating shared value. *Harvard Business Review*. 2011;89:62–67.⁷³

Having developed the concept of the value chain, as it relates to the creation of value along the supply chain, Michael Porter now proposes that value created should be shared with the society. Not only does this fulfill the social responsibility of the enterprise, but this may also be really good for business, with the power to unleash the next wave of global growth. Porter argues that societal needs, not just conventional economic needs, define markets, and social harms can create internal costs for firms.

Porter defines “shared value” as policies and operating practices that enhance the competitiveness of a company while simultaneously advancing the economic and social conditions in the communities in which it operates. Shared value creation focuses on identifying and expanding the connections between societal and economic progress. Shared value occurs by reconceiving products and markets and by redefining productivity in the value chain. For example, a company can address specific social concerns, such as water and energy use, employee health and worker safety, environmental impact, and supplier access and viability, as they relate to the specific products or services that the company produces. Whereas corporate social responsibility (CSR) is pursued separate from strategy and is determined by external pressures of sustainability, philanthropy, and citizenship, creating shared value (CSV) aligns social and economic needs to compete more effectively and to maximize profits. CSV is based on a company-specific agenda, internally generated, to realign the strategy of the entire enterprise.

Porter believes that CSV represents the evolution of capitalism, entirely consistent with Adam Smith’s “invisible hand.” Shared value benefits both the community and the enterprise. This self-interested behavior yields profits that create social benefits, rather than diminish them. Economic value is created by the commitment to generating social value.

progressive economist at Columbia University, and Muhammad Yunus, winner of the Nobel Peace Prize for his work on microfinance in India, both contend that we have both the resources and technology to end extreme poverty during our lifetimes. Part of the answer to eradicating extreme poverty is improving the health of those 2.5 billion people who exist at the “bottom of the pyramid” (individuals who live on less than \$2.50/day). Optimizing global health is possible with improved water purification systems, agricultural alliances to improve supply chain logistics, regulation of markets to eliminate corrupt middlemen in local markets, access to medical supplies such as antibiotics and antiretrovirals, and establishing microcredit and microloans. Once again, sustainable health endeavors are not only desirable from an ethical perspective, but such ventures can open new markets and new opportunities for investment.

Human resource management

“A small group of thoughtful people could change the world. Indeed, it is the only thing that ever has.”

Margaret Mead

Perhaps one of the most important, least appreciated, and often neglected components of business administration is human resources management (HRM) (Box 5.10), which can

be defined as that component of an organization that strategically manages the value chain of human capital.³⁵ Although employees cannot be considered an asset of a company, workers at all levels provide the critical steps of adding value to the product or service, as inputs are converted to outputs. Furthermore, employees, as well as customers, can be an incredible reservoir of innovation, if this resource is managed appropriately, in terms of recruiting, developing, retaining, and promoting talent. HRM is so critical to the success of an organization that HR practices often dictate the culture of that business and provide competitive advantage in and of itself, by attracting people of the highest quality and best fit. At Google, for example, employees are encouraged to spend 20% of their time on projects outside of their line of responsibility; such an environment fosters controlled experimentation and is directly responsible for that company's rapid ascent in the world of information technology.

Managing people is a daunting responsibility and when done correctly, looks effortless, but when not done well, creates a workplace that stifles creativity, undermines quality, and detracts from the value proposition of the company. As complex as managing human capital is, several best practices have emerged that can be shared:

1. Leadership starts with self-awareness.
2. Communication with employees is a central role of the manager.
3. Effective managers can articulate their own values and vision.
4. Effective managers foster an environment that brings out the best in others.
5. Effective managers are willing to engage in difficult conversations about difference.
6. Effective managers understand how groups work and focus on creating a culture of performance, with defined metrics, that enhances teamwork and collaboration.
7. Effective managers are change leaders.
8. Effective managers learn, reflect, and renew.

In healthcare, HRM often focuses on "workforce development", which refers to the continuing education and training of employees for current, new, and changing jobs. What a nurse does today may be very different from what he or she will do in the future, and employees must be able to adapt to the changing models of healthcare delivery. Not only must healthcare providers deal with changing technology and evolving systems of healthcare, but also these employees must be able to work well with people of different educational backgrounds, different generations (traditionalists, baby boomers, gen Xers, and millennials), and different work/life balances. Diversity in the workplace no longer refers to people of different cultures, but recognizes different values, work styles, and needs.

What HRM leaders have discovered in healthcare is that investing in the organization's people has a far greater ROI than trying to recruit superstar candidates for specific jobs. Furthermore, treating employees like customers, as well as customers as employees, is the key to both retaining providers and patients. Provider and patient satisfaction is very important, not only in the rankings of healthcare systems, but also in future revenue streams. Very satisfied patients will continue to seek healthcare with their same providers and will refer

BOX 5.10 Idea watch: human resource management

Reference: Fernandez-Araoz C. 21st century talent spotting: why potential now trumps brains, experience, and "competencies." *Harvard Business Review*. 2014;92:46–56.⁷⁴

The value of developing human capital, to increase the competitive advantage of an organization, cannot be overstated. Recognizing, recruiting, growing, and retaining talent remains critical for the growth of an enterprise and the ability to fulfill its mission.

Given the volatility, complexity, and uncertainty that characterize the current markets, however, employees who are merely smart, experienced, and competent may not add as much value to a company as those who have the ability to continuously adapt to changing business environments. Managers seeking new talent to develop should focus on potential, not necessarily past performance, based on the following indicators:

- The right motivation
- Curiosity
- Insight
- Engagement
- Determination

their friends and family. Such marketing is priceless. This practice of stakeholder fulfillment is not only good business, but also great medicine.

Legal and regulatory considerations

"To live outside the law, you must be honest."

Bob Dylan

As might be expected, the legal and regulatory components of healthcare are so labyrinthine that these considerations could easily occupy the contents of an encyclopedia (Box 5.11). Nevertheless, the plastic surgeon must be aware of the broad categories that affect his or her practice and, most importantly, have a low threshold to seek legal counsel, when needed. In addition to knowing about malpractice law, healthcare providers must have some familiarity with contract law, labor relations, corporate structure and liability, rules of emergency medical treatment, scope of practice by non-physician providers, certificate of need for and accreditation of outpatient facilities, and protection of patient confidentiality. A comprehension of these issues is not only recommended but is necessary, as providers must comply with state and federal regulations or face investigation, legal expenses, fines, court time, or prison, depending upon the degree of culpability, intent, and involvement.

The purpose of this section, however, is to examine how regulatory and legal changes in the business world have recently impacted healthcare as a business.^{36–38} Understanding the macroeconomics of and market changes in healthcare, as a result of government intervention, will hopefully assist the healthcare provider in making more informed decisions when delivering healthcare. This section will not debate the benefits or detrimental effects of regulation, but will rather present the changes that have occurred, as objectively as possible.

Before discussing how recent regulation has affected the business of healthcare, it is important to review the basic forms of business ownership. A sole proprietorship is an

entity owned by one person, who assumes personal liability for debts incurred by the business. A partnership is a type of business in which two or more individuals agree to share profits but also liabilities; the advantage of such a structure, like that of a proprietorship, is that net income is taxed only once. A corporation is a business with a distinct and separate identity from its members; for-profit and not-for-profit corporations must be owned by multiple shareholders and are overseen by a board of directors, which manages the executive team. Most hospitals follow this model, while many physicians in private practice may function as a proprietor or as the head of an S-corporation. Finally, a cooperative is a type of corporation with limited liability whose members, in contrast to shareholders, share decision-making capabilities. One disadvantage of corporations and cooperatives is that profit is subject to double taxation: first on net income of the entity, after operating and indirect expenses are deducted, and second on the returns to the stakeholders, in the form of personal income, dividends, and other capital gains such as stock that is sold.

Sarbanes–Oxley Act, 2002

In response to such corporate and accounting scandals as Enron, Tyco, and WorldCom, as well as the “dotcom” bubble that burst and cost investors billions of dollars, both the House and the Senate overwhelmingly supported and passed the Sarbanes–Oxley Act (SOX).³⁹ Public confidence in the nation’s securities markets had been greatly undermined, and this legislation attempted to restore the stability of these markets, through oversight and control. In addition to creating a Public Company Accounting Oversight Board, SOX mandated that: 1) auditors could not provide consulting services to the same clients; 2) senior executives must take individual responsibility for the accuracy and completeness of their corporate financial reports; and 3) financial disclosures of public companies must include enhanced reporting of off-balance sheet transactions, assumptions for pro formas, and stock transactions of corporate officers. Although SOX did not have provisions directly dealing with healthcare, this act affected the healthcare industry, as every publicly held company involved with healthcare would have to undergo significant restructuring of their accounting practices. Proponents contend that such legislation was essential to strengthen accounting controls and restore investor confidence, while opponents cite the overly complex oversight necessary for compliance, leading to reduced competitiveness with foreign businesses.

American Recovery and Reinvestment Act, 2009

As the United States headed into the worst recession since the Great Depression, Congress passed the American Recovery and Reinvestment Act, in an attempt to create jobs, promote investment, and induce consumer spending.⁴⁰ Because the Federal Reserve had already decreased interest rates to zero, with little effect on the credit markets, fiscal policy was chosen over monetary policy as a plan to stimulate the economy, and therefore an infusion of government capital – \$787 billion – was utilized to bridge the output gap created by a fall in consumer spending. Although the majority of the capital was

used to fund projects and programs in energy, communications, education, and transportation, healthcare received \$151 billion, with the vast majority of this money used to support Medicare. In the wake of this stimulus package, the national economy has remained volatile but appears to have stabilized, and the demand for healthcare services has not decreased, as many economists predicted.

Patient Protection and Affordable Care Act, 2010

In a bitterly fought, highly publicized partisan struggle,⁴¹ Congress eventually passed the Patient Protection and Affordable Care Act (ACA), which is essentially a healthcare reform bill that focuses on health insurance reform.⁴¹ Described as the most significant overhaul of the US healthcare system since Medicare and Medicaid in 1965, the ACA was enacted to increase the quality and affordability of health insurance, lower the uninsured rate by expanding public and private insurance coverage, and reduce the costs of healthcare for individuals and the government. Benefits of this legislation include expanded Medicaid eligibility, subsidized insurance premiums, incentives for small businesses to provide healthcare coverage, prohibition of denials by insurance companies, establishing a market of health insurance “exchanges”, and financial support of medical research and information technology, such as the electronic medical record.

Critics insist that the proposed deficit reduction of \$143 billion, over the first decade, will be neither achievable nor maintainable. The cost of this plan is offset by fees on pharmaceutical companies and on medical devices, new taxes on high-income brackets, improved efficiencies from information technology, and reduced administrative expenses. The Supreme Court has upheld the constitutionality of the ACA on two occasions, affirming the legality of the individual mandate and the federal subsidy, but ruled that individual states cannot be forced to participate in Medicaid expansion. However, over a third of the 32 million uninsured adults from 2011 now have health insurance, dropping the uninsured rate from 18.4% to 11.4%, by mid-2015.

Dodd–Frank Wall Street Reform and Consumer Protection Act, 2010

Already considered the most sweeping change to financial reform since the Great Depression, the Dodd–Frank Wall Street Reform and Consumer Protection Act is designed to permanently fix the economic problems that the Stimulus Act helped to stabilize.⁴² The aim of the bill is as follows: “To promote the financial stability of the United States by improving accountability and transparency in the financial system, to end “too big to fail”, to protect the American taxpayer by ending bailouts, (and) to protect consumers from abusive financial services practices.” The impact on the financial regulatory system will certainly be far-reaching, with significant restructuring of the flow of capital within our economy. Specific targets of reform include hedge funds and other investment banking instruments, the Federal Reserve, Wall Street transparency and accountability, mortgage and commercial lending institutions, and consumer and investor protection programs. The question for the healthcare industry is not if the Dodd–Frank Act will affect healthcare delivery, but how.

BOX 5.11 Idea watch: legal and regulatory considerations

Reference: Thacker PD. Consumers deserve to know who's funding health research. *Harvard Business Review* online, December 2, 2014; <https://hbr.org/2014/12/consumers-deserve-to-know-whos-funding-health-research#75>

Serving as the lead investigator for Senator Charles Grassley, who co-authored the Physician Payments Sunshine Act of 2010 (an amendment to the ACA), Paul Thacker helped to expose previously undisclosed payments made by drug and device manufacturers to doctors and teaching hospitals, over the course of several decades. While much of this funding could be considered legitimate, to support research and education, much of the funding was not, covering such activities as the ghost writing of scientific publications, public speaking events in which content was biased, and kickbacks for using specific drugs and devices.

Perhaps the most important ramification of this legislation, which requires that industry report all financial transactions with physicians, is the improved transparency of this relationship, such that real and potential conflicts of interest can be identified. Optics matter. In exchange for our right to self-regulate as professionals, physicians must apply our specialized knowledge and skill to the greater societal good, conforming to a body of ethics that is built on honesty and integrity.

Thacker's hope is that given medicine's leadership position in disclosing industry funding, it is time for physicians to lead their other colleagues in science to ensure that all scientific work remains transparent and independent. While the Sunshine Act remains controversial, and long-term effects are not known, there has been a shift toward transparency at the intersection of industry and medicine. We now recognize that all physicians face conflicts of interest, which should be managed proactively, if possible.

Negotiation

"You can't always get what you want, but if you try sometime, you just might find, you get what you need."

Mick Jagger and Keith Richards

Negotiation (Box 5.12) can be defined as "a dialogue intended to resolve disputes, to produce an agreement upon courses of action, to bargain for individual or collective advantage, or to craft outcomes to satisfy various interests".⁴³ Whenever a decision is made, negotiation occurs. If a surgeon decides to start a laser practice, he or she must examine the opportunity cost in pursuing that service and negotiate, with the stakeholders of his or her practice – receptionists, nursing staff, patients – how this change will impact the practice. If a junior partner wants to develop a microsurgical breast reconstruction practice, he or she must negotiate with the hospital for more operative block time, carve out with insurance companies a more favorable reimbursement schedule, and gain the blessing of the senior partners, who will have to cover these patients when the primary surgeon is not available and absorb these low margin cases into their revenue stream. If an academic plastic surgery practice wishes to develop and build an outpatient aesthetic center with procedural rooms, the division chief must perform a complex negotiation with multiple parties (the Dean, Chairs, hospital administrators), over multiple iterations, regarding multiple issues.

Although some individuals are blessed with excellent empathic and communication skills and can negotiate successfully, negotiation is a discipline that can be learned.

Practice and preparation are the keys to success. The field of negotiation, as an academic discipline, is a rich body of work that incorporates game theory, auction strategies, psychology, and behavioral economics. Perhaps the seminal work in this field is *Getting to Yes: Negotiating Agreement Without Giving In* by Fisher, Ury, and Patton.⁴⁴ The two overriding principles are: 1) knowing what you want versus what you need and 2) knowing what your opponent wants and needs. Negotiating begins with considerable preparation, not just predicting what your opponent will do, as if in a chess match, but what your opponent requires to improve his or her position. In fact, both opponents in a two-party negotiation may not even know what their best position is or why a certain solution may be favorable for each other. Creativity and communication are critical for success.

Negotiation, then, begins by developing and articulating your BATNA: the best alternative to a negotiated agreement. This is the walk-away position if no agreement can be reached, or "the lowest you will go", which should be ascertained before the negotiation begins. After deciding that you will not bargain over these positions, utilize the following four principles: 1) separate the people from the problem; 2) focus on interests and not positions; 3) invent options for mutual gain; 4) insist on using objective criteria.^{45–49}

These concepts of "principled" negotiation work most of the time. Occasionally, however, negotiation reaches an impasse, and breakthrough can be achieved by reframing the problem. Specifically, avoid escalation by not reacting, arguing, rejecting, or pushing. Step out of the situation, help the other side view the problem objectively, and reframe the problem from their perspective. Determine what options will provide mutual gain, or at the very least, minimize losses. In other words, pick your battles wisely. Concession is not failure, but often resets the parameters of the problem, so that future iterations of the "game" may yield an outcome in your favor.

Particularly difficult negotiations involve those individuals or groups who will not compromise over their demands, who have an asymmetry of information, who are unwilling to view the problem from your perspective, or who threaten to use power to enforce their solution. People who fall into this category are the schoolyard bully, an impaired physician, sociopaths, terrorists, and sometimes the "difficult patient", who may have an underlying body dysmorphic disorder. One

BOX 5.12 Idea watch: negotiation

Reference: Mikes A, Hall M, Millo Y. How experts gain influence. *Harvard Business Review*. 2013;91:70–74.⁷⁶

Is it better to be loved or feared? Effective negotiation can be accomplished by following a set of rules and guidelines, but how does one achieve influence on the decision-making of others? Projecting strength and warmth surely helps in the art of persuasion, but the authors of this paper identified four competencies that allow individuals to gain personal and organizational-wide influence:

- Trailblazing: finding new opportunities to use expertise
- Toolmaking: developing and deploying tools that embody and spread expertise
- Teamwork: using personal interaction to take in others' expertise and convince people of the relevance of your own
- Translation: personally helping decision-makers understand complex content

option is to not negotiate – step away from the situation – and use other means to resolve a dispute, such as legal action. However, skilled negotiators can still deal with these challenging situations effectively, by using uncertainty, chaos, and ambiguity to disarm opponents and neutralize their position. Successful negotiators can translate little gains into positive momentum, by focusing on future rounds of the negotiation and setting up more effective positions for the future.

Ethics

“Always do right, this will gratify some people and astonish the rest.”

Mark Twain

In healthcare, we are faced with multiple challenges that test our ethical grounding (Box 5.13). Healthcare providers must make numerous decisions regarding patient care every day, and society rightfully expects these providers to behave ethically. Competency in patient care and medical knowledge is required but not sufficient; providers must also demonstrate competency in interpersonal and communication skills, systems-based practice, practice-based learning, and professionalism, all of which involve a firm commitment toward ethical practice. So important are these competencies that medical education, residency training programs, state licensure, board certification and maintenance of certification, and hospital credentialing incorporate these elements in evaluating healthcare providers.

John Canady, past president of the American Society of Plastic Surgeons and former chair of its Ethics Committee, observed, “Plastic surgeons who are aware of competing interests that influence their decision-making processes stand a greater chance of achieving ethical outcomes. Nevertheless, with the growing volume of non-reimbursed care and expectations of perfect outcomes, achieving uniformly ethical decisions without burdensome self-sacrifice is difficult at best”.⁵⁰ Competing factors that influence decision-making for plastic surgeons include personal finances (ownership of surgery centers, selection of procedures, pricing), regulatory forces (Emergency Medical Treatment and Active Labor Act (EMTALA), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), American Association for Accreditation of Ambulatory Surgery Facilities (AAAASF)/Accreditation Association for Ambulatory Healthcare (AAAHC), Occupational Safety and Health Administration (OSHA), and Health Insurance Portability and Accountability Act (HIPAA) – to name just a few, and professional duty (informed consent, discussion of error).

When faced with a dilemma, healthcare providers must incorporate intuition and reasoning into making a decision. Resolution of an ethical question often requires careful consideration of culture, infrastructure, leadership/governance, and personal integrity. Ethical intelligence can be developed. In his book *Strengthening Ethical Wisdom*, Jack Gilbert argues that intentions, manifest by vision, mission, values, strategy, and goals, directly impact performance.⁵¹ In healthcare, this translates into patient safety, quality of care, productivity and throughput, patient and employee satisfaction, reputation, and financial health. Medical ethics is practical, case-based, and relative to the context of the situation.

Just as ethics helps to guide decision-making in healthcare, so too should ethics play a major role in the choices made by business entities. The history of ethics and capitalism is quite fascinating. Adam Smith, who published *The Wealth of Nations* in 1776, argued that markets were guided by “the invisible hand” to produce the right amount of goods for society, but that such a force was intimately tied to our ethical obligations to each other.⁵² Andrew Carnegie and other industrialists from the 1800s articulated the need for business to pursue charity and stewardship, both forms of social philanthropy, because with power comes responsibility. Even Milton Friedman, the Nobel-winning economist from the University of Chicago, who believed that the only ethical obligation of business is to maximize profits, emphasized that business efficiently creates

BOX 5.13 Idea watch: ethics

Reference: Anderson M, Escher P. *The MBA Oath: Setting a Higher Standard for Business Leaders*. New York: Portfolio Hardcover, the Penguin Group; 2010. <http://mbaoath.org>.⁷⁷

In response to several highly publicized business scandals of the early 2000s, academic leaders in business management have come forward to develop the MBA Oath.⁵³ The integrity of business, as a “profession”, was seriously compromised, involving fraudulent accounting (Enron), Ponzi schemes (Bernie Madoff), excessive executive compensation (widening of the salary gap between leadership and labor), business–government collusion (the revolving door between academia, Wall Street, and the Federal Reserve), and illegal derivative trading (one of the many causes of the Great Recession of 2008–2009). Similar to the Hippocratic Oath for physicians, this pledge acknowledges that management is a profession bound by ethical principles.

The MBA Oath

As a business leader I recognize my role in society.

- My purpose is to lead people and manage resources to create value that no single individual can create alone.
- My decisions affect the well-being of individuals inside and outside my enterprise, today and tomorrow.

Therefore, I promise that:

- I will manage my enterprise with loyalty and care, and will not advance my personal interests at the expense of my enterprise or society.
- I will understand and uphold, in letter and spirit, the laws and contracts governing my conduct and that of my enterprise.
- I will refrain from corruption, unfair competition, or business practices harmful to society.
- I will protect the human rights and dignity of all people affected by my enterprise, and I will oppose discrimination and exploitation.
- I will protect the right of future generations to advance their standard of living and enjoy a healthy planet.
- I will report the performance and risks of my enterprise accurately and honestly.
- I will invest in developing myself and others, helping the management profession continue to advance and create sustainable and inclusive prosperity.

In exercising my professional duties according to these principles, I recognize that my behavior must set an example of integrity, eliciting trust and esteem from those I serve. I will remain accountable to my peers and to society for my actions and for upholding these standards.

This oath I make freely, and upon my honor.

and allocates wealth in society if the stakeholders are honest, transparent, and just.

Today, business ethics is just good business. A new paradigm for delivering stakeholder value has replaced the previous model of maximizing shareholder returns. Because suppliers, customers, employees, competitors, and communities are all affected by the decisions of a business, a stakeholder-approach to organizational structure maps out these relationships and attempts to align competing interests, to maximize value creation of the networks, products, services, and information. Most business leaders are aware that values, rights, duties, and responsibilities must inform decision-making, much like these principles affect medical ethics. Consequences may not only have legal ramifications but may also impact the bottom line. Values-based capitalism strives to maximize stakeholder wealth by trying to humanize the institution of business and encourage stakeholders to perform at their best, not their worst. Key principles of values-based capitalism include: stakeholder cooperation, shared responsibility, recognition of complexity, continuous creation, and emergent competition.

Leadership

"The greatest accomplishment is not in never failing, but in rising again after you fall."

Vince Lombardi

The most concise answer to the question "what defines a leader?" is "someone who has followers." The real question, though, should be framed as follows: "what defines a great leader?" This answer is quite elusive, depending upon the leader, the context, and the constituents (Box 5.14).⁵⁴

In business, leaders must first and foremost be effective managers (Fig. 5.9). "The manager is the dynamic, life-giving element in every business. Without leadership, the 'resources of production' remain resources and never become production. In a competitive economy, above all, the quality and performance of its managers determine the success of the business, indeed they determine its survival. For the quality and performance of its managers is the only effective advantage an enterprise in a competitive environment can have." So begins *The Practice of Management*, published in 1954 by

Peter Drucker, considered to be an early, defining modern work on management theory and practice.^{55,56}

Although managers differ from leaders along many parameters, the skill sets of both are complementary and, when combined, provide synergy that enhances the strength of an organization:⁵⁷⁻⁶²

Managers administer	Leaders innovate
Managers ask how and when	Leaders ask what and why
Managers imitate	Leaders originate
Managers focus on systems	Leaders focus on people
Managers maintain	Leaders develop
Managers rely on control	Leaders rely on trust
Managers accept the status quo	Leaders challenge the status quo
Managers look at the bottom line	Leaders look toward and past the horizon
Managers do things right	Leaders do the right thing
Managers operate	Leaders strategize
But, managers often lead	Leaders often manage

Drucker continues, "To succeed in this new world, we will have to learn, first, who we are... Success in the knowledge economy comes to those who know themselves – their strengths, their values, and how they best perform". Individuals must determine where they belong and what they should contribute. In this age of discontinuity, where information has become as valuable as capital, and communication is critical to the flow of adding value, individuals must manage their own careers, carving out discrete niches, keeping themselves engaged, and knowing when to change course.

For leadership to be effective, the individual uses social influence to gain the support of followers, through positional, personal, and relational power, to accomplish a common goal. Many theories have been proposed to describe exactly how leadership works, but ultimately leaders must be responsible for a number of functions, such as delegation, empowerment, negotiation, conflict resolution, innovation, inspiration, and guiding change. Through a variety of leadership styles – forcing, avoiding, compromising, accommodating, and collaborating – leaders must also learn how to "manage from the middle". Serving as a conduit for transfer of information, knowledge workers today must manage up and down, both their supervisors and their direct reports. Those who can effect change in such an environment are incredibly influential, adding value to the human capital of an organization.

Perhaps the most critical function of a leader is the building of high-functioning, high-performing teams. Teamwork has become increasingly important in business, because of several factors: environmental complexity and pace, the dependence upon internal and external partners, the need for multiple sources of information, and the desire to have varied perspectives and diverse thought. The smartest of us is not as smart as all of us. Teams, however, do not automatically form and function smoothly. An effective leader builds collaborative teams that deliver results by establishing the following characteristics: goal compatibility, trust and commitment, interdependence and accountability, open communication and acceptance of ideas, and converting conflict into creativity. The leader also serves as the team's advocate, gaining support from senior executives, providing the necessary resources to

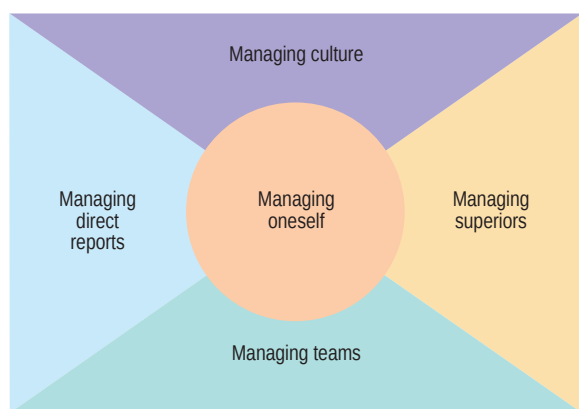


Fig. 5.9 Leadership: leading the new venture.

solve the problem, and keeping stakeholders informed. It turns out that being an effective team leader has less to do with technical knowledge and more to do with emotional intelligence and communication skills.⁶¹

Kouzes and Posner offer a simple but extremely helpful model of leadership in which credibility serves as the foundation for all future success. Having studied hundreds of leaders across many types of disciplines, they provide these recommendations for becoming a great leader: 1) model the way – clarify values and set the example; 2) inspire a shared vision – envision the future and enlist others; 3) challenge the process – search for opportunities, experiment, and take risks; 4) enable others to act – foster collaboration and strengthen others; and 5) encourage the heart – recognize contributions and celebrate the values and victories.⁶⁰ This model dispels the myth that “it is lonely at the top”, because the goal of leadership should be to bring everyone to the top.

Leadership at the very top – CEOs of large, complex organizations – no doubt requires social influence to achieve goals, but this type of leadership also contains unique challenges that require unique skills, to deliver effective direction and strategy, organizational structure, selection of people, and appropriate incentives. Porter and Nohria examined 110 newly appointed CEOs from mostly public companies, with median revenue of \$3.7 billion.⁵⁴ Average age at appointment was 49.7 years, and average time with the company had been 14.1 years. Seventy-five percent of these CEOs had been inside candidates, and 64% had a graduate-level degree.

The findings were surprising. Challenges specific to their new role as CEO included broader scope than anticipated, placating the Board of Directors, constraints in power, difficulty obtaining reliable information, maintaining visibility, having to produce within a limited time horizon, and expectations of change by the stakeholders. These CEOs discovered, however, that indirect levers could be quite powerful, by shaping context so that members of the organization could make good decisions, take appropriate action, and advance the mission of the company. Other interesting findings included:

Time spent working on issues internal to the company:	69%
Time allocated to core agenda items:	52%
Time spent in face-to-face communication:	81%
Time spent with constituents other than direct reports:	42%
Time spent communicating with groups:	63%

Based upon these observations, specifically that indirect levers of influence may be more important than direct levers, Porter and Nohria recommend that CEOs pay special attention to allocating their most limited, yet crucial resource: their presence. CEOs – and perhaps all leaders – can manage their presence by setting a clear personal agenda, communicating relentlessly, gathering information continuously, leveraging symbolism, and harnessing the power of a strong management team. Establishing legitimacy, through competence, fairness, results, and integrity, instills confidence in the stakeholders, who are then empowered to do their best.

BOX 5.14 Idea watch: leadership

Reference: Goleman D. The focused leader: how effective executives direct their own – and their organizations’ – attention. *Harvard Business Review*. 2013;91:50–60.⁷⁸

Dan Goleman introduced the idea that effective leaders must have emotional intelligence, but he now adds the skill of focus to the list of qualities that distinguish the best leaders. He points out that a primary task of leadership is to direct attention, and as such, the leader must first learn to focus his or her own attention. Furthermore, the concept of focusing is not just filtering out distractions, but rather concentrating on different topics, in different ways, for different purposes. Goleman cites recent neuroscience research that shows that focus is a complex cognitive function that draws upon the integration of multiple neural pathways.

To be effective and sharpen one's focus, every leader must cultivate an awareness of self and others. Both inward and outward focus are necessary to develop one's emotional intelligence. Self-awareness and self-control increase one's ability to focus on others. Social relationships are dependent upon directing attention toward others, and empathy emerges as the critical trait that is the hallmark of a natural leader, regardless of organizational or social rank. Goleman notes that the most effective leaders actually exhibit three types of empathy:

1. Cognitive empathy – the ability to understand another person's perspective
2. Emotional empathy – the ability to feel what someone else feels
3. Empathic concern – the ability to sense what another person needs from you.

The ultimate challenge of any leader is to take their organization from “good to great”. Jim Collins identified 11 publicly traded, stable companies that experienced substantial, sustained growth, as defined by financial performance several multiples better than the competitors in their industry.⁵⁸ Collins identified specific factors responsible for helping transition from “good to great”: focusing on core competencies, forging a culture of discipline, finding the right people to figure out where to go, confronting the brutal facts while maintaining hope, using technology accelerators, and creating momentum from the additive effect of small initiatives. What all of these companies had in common, though, was Level 5 leadership: CEOs who had personal humility and professional will. The most effective leaders were not outspoken and charismatic, but rather humble, selfless individuals who displayed fierce resolve in delivering the company's value proposition. Integrity and vision matter; these qualities confer upon the leader the ability to transform an organization from good to great.

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Medico-legal issues in plastic surgery

Neal R. Reisman

SYNOPSIS

- Plastic surgeons will have a significant interaction with attorneys as they care for the injured, abused, and possibly negligently treated.
- Informed consent is a process, not merely a signed document.
- An express warranty may be established by including in the record a photo the patient believes will be the result.
- Fraud and abuse claims have NO statute of limitations and are not covered by liability insurance.
- HIPAA is created to protect patient privacy and covers medical records and photography.
- Agency Law places responsibility on the employer for employee negligence when performing work-related duties.
- Divulging patient information in a blog or social media website is an HIPAA violation.
- It is critical to notify your liability carrier as soon as possible if you receive notice of a lawsuit against you.
- Physicians who basically share an office may each be exposed to liability in caring for patients.
- Patient selection, when proper and appropriate, is the best method to avoid a negligence claim against you.

Introduction

Plastic surgeons have many interactions with the legal system. While medicine has many nuances and inferences, the law is steeped in legal doctrine, and the written word. An impression causing considerable concern is that if something is not recorded and written, it never occurred. The practice of medicine is filled with usual actions that may not be specifically documented, leading to a major conflict between medicine and the law. This chapter will focus on the interactions between plastic surgeons and the legal system and also methods of reducing medico-legal risk and improving patient

safety. Areas of the law will be presented and its impact on plastic surgical practice will be emphasized.

Interactions with attorneys and the legal system

Plastic surgeons can have a significant interaction with the legal system through their care of patients, which through injury and disease, may lead to legal representation. Work-related injuries, auto-accidents, animal bites, and domestic abuse often will initiate a lawsuit. The physician will participate in documenting injury, future medical expenses, and commenting on disability and scarring usually through a deposition and occasionally live testimony at trial. There are those who abhor any interaction with attorneys, but realistically many feel it appropriate to participate in the legal system and certainly represent and assist their patient. There are some guidelines and rules to follow. The Health Insurance Portability and Accountability Act (HIPAA) now requires written consent before you can discuss any patient information with anyone outside of the medical treatment area. An attorney acting within ethical guidelines will provide you with an authorization by their client and your patient to discuss the patient's care and treatment. You are prohibited from discussing the patient's information without such authorization. Do not be fooled by legal-appearing or court-initiated papers that seem to override written approval. Ask the attorney for authorization and confirm with your patient as necessary. If a deposition is required, assure that you have proper written authorization.

It has also been suggested if you are hired as an expert, that you seek advanced payment for your time and establish a written agreement that if the deposition is canceled more than 2 weeks from the scheduled date, you will refund the payment. If the deposition is canceled in the second week, then one half of the payment will be refunded, and if it is canceled closer

to the scheduled time, the payment will be forfeited. Establish an hourly rate and seek 2 hours in advance. It is also wise to schedule a deposition at the end of the day and not in the middle, which could significantly interfere with patient scheduling.

Legal interactions: depositions and narratives

Much of the correspondence between the plastic surgery practice and an attorney may be in their request for an official narrative outlining care, past treatments, future concerns, and specific questions the attorney might pose. The medical narrative should be factual and list what sources are used and what the report is based on. One should be honest in describing past and future concerns and not be too overreaching or inadequate in description. It is common to cite that your opinions are based on a review of certain documents, discussions with the patient, and the conclusions are based on training and experience. Depending on state law, there is usually a customary fee for such a narrative, which should be collected in advance of any dictation to the record. It is important to cite when references are used, for it is not uncommon to be given certain documents to help influence your opinion. When all these documents are subsequently reviewed, opinions may differ from the original narrative, which can now be explained by specific lists of information reviewed.

Areas of the law

There are many areas of the law that have an impact on plastic surgical practice. Most will include a claim of negligence, which initiates your malpractice insurance. Other claims either strengthen the malpractice claim or add additional claims that are not covered by your malpractice insurance; all are intended to add additional pressure to settling the suit.

Tort law: negligence, malpractice

Tort law is the basic area of the law covering negligence and malpractice. There are four requirements of the negligence action. The first area is a duty to provide care and acts in question. The second is that duty is breached, usually in a sub-standard way. The third requirement is that the breach is directly responsible for whatever damages occur. This is called proximate cause. And the fourth requirement is that there are damages as the result of the prior three requirements. The proof and arguments surrounding these four elements comprise a malpractice claim. Other legal interactions will also involve your testimony establishing these four elements. An example would be a dog bite resulting in a lawsuit. You have surgically repaired the laceration and now must testify that this injury is from the dog and the damages that you describe are directly the result of the bite. While this may appear ridiculous, as these questions are posed to you, you can now see that the three elements of this tort case can be established. The first element of that duty might be to protect people from the dog.

Informed consent

The doctrine of informed consent is a necessary part of both legal interactions and patient care. There are two standards

utilized for informed consent. A few states utilize the reasonable “doctor standard”, which states that information a reasonable physician thinks is important must be presented to a patient for their informed consent. More commonly, a reasonable “patient standard” is used. The standard states that all information a reasonable patient would want and need to know should be presented as they make their informed choice. There is much confusion about how much information should be outlined and in what fashion. There are those who believe the informed consent process should be videotaped as there is always a question after-the-fact about what was discussed or presented. This is usually unnecessary as documentation should include the process of information presented, questions asked and answered, and finally an understanding of what the physician can and cannot do. There are many styles of learning and current thinking is to include three styles during the informed consent process. There are visual learners, auditory learners, and kinesthetic learners. The visual learner would want to see a picture, photograph, or some demonstrative example of what is being proposed. The auditory learner wants to listen very carefully to recommendations, the surgical procedure, pre- and postoperative instructions, reasonable expectations, alternatives to care, and inherent risks and complications. The kinesthetic learner is looking for how all of this affects them personally. The goal of informed consent is reaching high levels of understanding, which may be reached by combining all three learning styles throughout the process of informed consent. It is not a signed document itself, but the process of understanding documented by the consent. I believe the surgeon has a responsibility to outline the risks and hazards of the proposed procedure. It is also suggested to develop a team of surgeon, nurse, coordinator, and others to achieve this goal. There are some patients who never reach a complete understanding of the informed consent process and it is recommended that surgery then should not proceed. It is also recommended that multiple visits and discussions be utilized allowing appropriate time for discussions at home, reflection on goals, and adequate questions to be answered before proceeding with a nonemergent procedure.

Privacy law

Privacy law is intended to protect patient information. This includes their medical information, photographs, lab results and correspondence. HIPAA covers many protections for the patient. The practice has an obligation to explain and document the patient’s understanding and acceptance. There is a duty to secure their information, and even pursue those who violate such protections. The practice will have an obligation under new “red flag rules” to check identity of patients with their coverage, further protecting the patient against identity theft. The plastic surgery office must be careful when using patient information or photography in a commercial way, such as on a website, advertisement or patient outcome booklet, shown to prospective patients. A breach of privacy is not covered by your malpractice insurance and any judgments as a result of this breach must come from you alone and not your insurance company. It is not unusual to have a claim joined to a negligence claim that patient information was not protected. This often adds to the stress of a lawsuit and may add incentives to settle the claim. If you have patient

permission to show such information, a specific written consent for commercial use must be signed by the patient. You can help yourself and your practice by adopting HIPAA rules,¹ identifying a “red flag” office employee who can safeguard patient identity, and being very diligent about obtaining consent forms for treatment, release of information, specific commercial use and photographic consents. Areas of concern are thus social networks and blogs, such as Facebook and Twitter. There is risk of a surgeon or practice describing “a day in the life of a plastic surgeon” on a blog, but that day’s patient may recognize him or herself, even though no name is mentioned. There is metadata embedded within a photograph that remains despite a file name change. It is important to “scrub” or remove the metadata before posting or displaying any photograph even with specific written commercial consent. The metadata may become visible when a mouse is used to highlight a photograph even if named to prevent disclosure. The HIPAA consent for treatment and documentation such as photography is inadequate when the photograph is to be used to promote the surgeon’s website, even if for educational value. The specific commercial consent must list specific uses, length of time, where it is to be posted, and other distributions. It is also a help to seek a Communication permission from the patient outlining and documenting how they may be contacted, either by cell phone, texting, regular mail, at work or home or any type of social media.

Warranty law

Warranty law involves two specific types of warranty issues; “express warranty” and “implied warranty”. You should understand that warranty issues are not covered by your malpractice policy. An express warranty utilizes a demonstrative part of the record to create a guarantee towards a result. This can be accomplished by including a photograph that the patient brings of a result they seek, or it may change created results that are made a permanent part of the business record. It is well accepted among physicians that there are no warranties or guarantees towards a result, since healing can be so specific and usually out of the physician’s control. While the visual aids are important in educating the patient about procedures and expectations, the practice should be very careful not to establish a guarantee of a certain result. Patients seemingly have unrealistic expectations, as the media and other factors portray certain social appearances. Utilize all educational tools including imaging to help the patient understand the procedure and the results but make sure you have both a disclaimer and documented discussions concerning realistic expectations.

The implied warranty can be more difficult. This is not based on something added to the chart that is tangible but rather an understanding that the patient presents to you that you must consider and address. Examples might be the fact that two weeks after a major surgery, the patient is expecting to travel to a family or business retreat. There is a possibility that the patient reasonably may be able to attend such a function, but are you willing to guarantee they will heal appropriately to do so? This becomes the main issue of these implied warranties. The patient discloses a requirement that they present. You should be careful to disclose and document the many reasons that might interfere with their requirement. Possibly changing the date of surgery or other considerations

should be addressed. If nothing is discussed or documented, and the patient misses their major event, it could be judged as your fault and you would be responsible for any financial losses they incur. This is becoming more common, as patients seek and demand quicker recoveries, adding procedures at the last minute, all within a shorter and shorter timeframe. Implied warranties could arise from time issues, financial estimates and costs, future care and treatments, and issues concerning results and expectations. Make sure the entire office team discusses patient comments and interactions because it is not uncommon to have a patient disclose varied demands to a receptionist or coordinator and never mention them to the surgeon. Include a paragraph in your informed consent document as well as your financial agreement that no warranties express or implied are present and that the patient understands and agrees with this.

Product liability

Product liability issues cover the increasing number of products we distribute, utilize or prescribe. There are many areas within product liability that would expose the practice. Those arising from negligent use of a product may have claims falling within their malpractice policy. Other misuse of a product or altering a product by placing on your private label may elicit additional claims not covered by your malpractice policy. Any device, product, or prescription that is given to a patient should include full instructions, risks, hazards, and alternatives. A key factor in this area is that liability is created in the foreseeable stream of commerce. That is when you give a sample of a skincare product to your patient; it is foreseeable that they might share that with family members and friends. It therefore becomes important to provide good safety instructions as to its use, allergies if any, and concerns of treatment, and document those in the record. When their friend uses the product and has a reaction, you may be responsible, even though you have never seen the friend as a patient. Adding private labels to the product may hide important ingredients and instructions. You should be careful to maintain such important information. Altering the product, even as simply as putting your name on it, may eliminate the manufacturer’s responsibility to defend you for using it appropriately. Be careful and investigate what are FDA approved uses for the product and/or device. Be cautious when industry reps suggest a different use without providing you with written approval. A physician has the ability to prescribe off-label but some precautions are necessary. The three necessary elements for off-label use are: (1) that the product is approved by the FDA for use; (2) that the proposed use is not experimental; and (3) there should be written confirmation of the patient accepting and understanding the off-label use.

Fraud and abuse

Fraud and abuse can definitely turn a winnable malpractice case into one that has to settle or is lost. Fraud is defined as the intent to deceive and abuse is defined as the intent to confuse. There are multiple ways in which fraud and abuse can be a part of a plastic surgery practice. Not only can fraud and abuse have a very negative effect on the outcome of a malpractice case, but in many states, a fraud conviction can

both jeopardize your medical license and involve criminal activity. One way of avoiding the perception of fraud is to assure your medical billing and coding conforms to your operative record and treatment notes. It is generally understood that the codes used for billing can be changed as an ongoing process. You must be consistent when adjusting the billing codes to reflect ethically on the procedures and treatments performed. Another area of exposure to fraud is the medical record. Altering a medical record can also expose you to both civil and criminal penalties. There are many ways to disclose an altered record that you should be aware of.

One technique involves an ESDA test, which measures pressure indentations on a page. An ESDA (electrostatic detection apparatus) is a piece of equipment commonly used in questioned document examination, to reveal indented impressions on paper, which may otherwise go unnoticed. It is a nondestructive technique (will not damage the evidence in question), thus allowing further tests to be carried out. It is a sensitive technique, and has been known to detect the presence of fresh fingerprints. When writing is fashioned on a sheet of paper resting upon other pages, the impressions produced are indented onto those below. It is these indentations which are detected using ESDA, thus allowing a match of the original document to its source (such as a ransom note, or a threat to extort) to the offender's notepad.

Where two or more handwriting styles can be found mixed into a single document, and features of one handwriting style depart from the features of the other, ESDA can help reveal the differences in pressures employed between the individuals responsible for the writing samples, otherwise unified on a single exemplar. An indentation on the page below can be evaluated to show corrections, additions, and other information about writings. A hospital chart has the most recent chronology on the top with past recordings on the bottom. When the patient is discharged, the chronology is reversed with the earlier dates on top and later dates on the bottom. Consequently, if there is a pressure indentation on a later date's page, that entry was made after the patient was discharged, which is altering a record.

Another method of documenting record alteration is analysis of the inks used. Each ink is dated and it is possible to confirm suspicions by testing the date of a questionable record entry. Records are changed appropriately based on misstatements and incorrect entries. The proper method of correcting a medical record is to draw a thin line through the misstatement allowing readability in addition to making an entry contemporaneous to the correction date and time in the record. Both entries should be initialed and date and time confirmed.

A further example of potential concern occurs when multiple procedures are performed necessitating two operative reports. The patient has carpal tunnel syndrome and is seeking liposuction. Her insurance through her business is self-insured and the employee health representative is a gossip, so she asks you to not disclose the liposuction to her company. The appropriate course would be to dictate two operative notes and make reference about each within each. The hand surgery operative note would make reference to an additional surgery to be dictated separately. The liposuction operative note would confirm prior hand surgery occurred and this procedure followed. A question of fraud or abuse that is deceiving or confusing would be to have no reference of both

procedures, possibly suggesting the total operative time was for the hand surgery alone.

Fraudulent concealment is yet another type of fraud that can plague the practice. If false or misleading information is given to a patient that they have been relying on, a fraudulent concealment claim may be generated. The significance of this is that it still is fraud, there is no malpractice insurance coverage, and it tolls, or extends the statute of limitations. That means if there is a 2-year statute of limitations after which an allegation claim is not valid, a fraudulent concealment issue can remove the statute's effect and render the claim still valid. An example where this may occur is in a lesion that is excised on the back with frozen sections showing removal of a squamous cell cancer with margins free of disease. The permanent section, however, and the final pathology report show tumor at the superior margin. This information is not disclosed to the patient who develops a recurrence; files a lawsuit 1 year after the statute of limitations would have prohibited such a lawsuit. A fraudulent concealment claim allows the lawsuit to proceed.

"Qui tam", part of the False Claims Act,² has the federal government rewarding fraud whistleblowers. Basically, a disgruntled employee files a false claim lawsuit against you, the employer, citing fraudulent claims, and the US government joins the lawsuit, allowing the whistleblower to collect a percentage of any judgment or settlement. This emphasizes the need for appropriate, ethical billing and coding, as well as eliminating disgruntled employees from the workplace.

Contract law

Contract law should have a limited role in plastic surgical practice. It is suggested to have a work employment contract with independent contractors, physicians in the practice, and aestheticians. Such an agreement would cover work-related requirements, ethical and legal standards, confidential and HIPAA requirements and other safeguards to the workplace. It is not uncommon for an aesthetician, employed by the practice, to quit and take all of the confidential patient information to their next place of employment. This is a direct HIPAA violation and there is a duty to retrieve and protect such information. Having a protective clause in your employment agreement prohibiting such an act is a further safeguard. Some states, such as California and Colorado, allow arbitration clauses as part of their state-wide tort reform. It can be attractive to establish such an arbitration required agreement in advance of surgery but it would not be legal to remove the patient's right to bring suit. One can argue further that the more a contract is established with a patient, the more likely a breach of the contract can be claimed when the results do not equal the patient's expectation. Contract law would be more of a problem in descending results and care than tort or negligence law. The patient merely has to prove that the contract was breached and their expected results failed, to collect money, whereas in a negligence action the physician must be proven to have acted negligently, which is usually more difficult to establish. A breach of contract merely requires that a contract be established and a party failed to fulfill their end of the agreement. Damages are paid to fulfill the contract. A negligence claim, however, requires a party to be negligent as to a duty of care, and damages are paid to compensate for

the negligent act. Develop an office policy manual outlining appropriate and expected care, as well as restricted and prohibited acts. Utilize an updated employment agreement for staff similarly outlining required and prohibited behavior.

We are observing an increase in “contract” personnel, often in the form of aestheticians, or operating facility staff, etc. The practice should be careful here in establishing guidelines for such individuals. This should be covered in an office policy manual. Contract personnel are not employees, and should have their own liability, not falling under agency law. This means you cannot totally manage their daily work, or cover them with insurance like the other employees. The issue of “control” over their work product is an important factor in labeling them as contract personnel or an employee; not the language used in their agreement. You should continually check on their licenses, malpractice history, and quality. You can provide them with the tools to perform their work, but not control their work such as you would with an employee. The issue is whether you will be responsible for their alleged negligence should a claim be made. The independent contractor is liable for their own negligence, while the employee through Agency law is your responsibility.

Regulatory issues within the law

There are many regulatory agencies overseeing a plastic surgical practice. The HIPAA is established to protect patient privacy and medical information. The patient should sign an acknowledgment of their privacy protection, and this is kept in the patient’s file. There are obligations to safeguard against identity theft, known as “red flag rules”.³ The practice must identify an individual to record each patient’s identity and inspect for procedures, billing, and insurance correspondence, to assure appropriateness throughout. This can include possibly copying the patient’s ID, such as a driver’s license or passport, including a photograph of the patient, and checking the above documents so they match the practice’s care and treatment.

The Occupational Safety and Health Administration (OSHA)⁴ covers office supplies and equipment assuring safety in the workplace. All supplies should be labeled with appropriate precautions marked, as well as a log of emergency treatment, should an accident occur. The FDA controls manufacturers of devices and products and although does not directly oversee physicians, there are requirements necessary for off-label use. Off-label use involves the nonexperimental use of an approved FDA device or product in a nonapproved fashion. Such use should have a specific consent documenting off-label usage and acknowledging patient acceptance. The practice should be very careful to only purchase FDA-approved supplies and avoid the temptation from frequent internet and mail solicitation for supplies that are “just like” those approved. Such a purchase would be illegal and could make the purchaser and practice subject to civil and criminal charges. State medical boards as well as state nursing and other regulatory agencies outline appropriate care in the office. It would behoove the practice to inquire about new standards and guidelines that apply. Ignorance is no excuse for inappropriate behavior. State board actions describe who can do what in an office environment and with what degree of supervision. It is very important for all staff and physicians

in the practice to understand and comply with these rules. It is unwise to ask an employee to care for a patient when it violates state rules. An example would be an aesthetician who was asked to inject Botox® when the state prohibits anyone but a physician, nurse practitioner or physician assistant to perform such an injection. Another example is to have your laser technician treat patients with you, the physician, out of the office and the state requires direct supervision of such treatments by a physician. If there is a bad outcome of such treatment, or anything that would trigger an investigation; it severely damages any defense raised and could void malpractice liability coverage. The practice must be vigilant in keeping up with the each state board rule and regulation, and decisions that affect a medical practice, nursing practice and others who participate in a plastic surgical endeavor.

Agency law

Agency law encompasses those in the workplace and their interactions. It is a doctrine that the employer is responsible for negligent acts of the employee during the scope of employment or in furtherance of the business. Any negligent acts by an employee are attributable to the employer. It therefore becomes important for the employer to outline what is acceptable and unacceptable behavior, usually in an “office policy manual”. Supervision becomes important, as claiming that one was unaware of risky or negligent behavior is no excuse and will not defer blame. You should have been aware of risky or negligent activity. However, violating the office policy manual that clearly defines what should not occur may help protect the practice against a liability claim. The practice should make attempts to avoid harassment in the workplace while developing a good team for communication with patients. Problem employees should be addressed promptly following the office policy manual as to counseling, disciplinary action, and termination. There should be documentation as to how these issues are addressed so if an ex-employee challenges their dismissal, the practice can support the decision.

There are many employee issues such as embezzlement, disruptive employees, employees who “steal” patient information, and have disagreements about hours, vacation and daily routines. All should be covered in the manual. Embezzlement can be potentially avoided by having a dual system of checks, say accounts payable and receivables matched against bank statements. One employee responsible for both sides may be a formula for theft. Develop written policy for hours, telephone, smoking, vacation days, and patient interactions that everyone agrees with, and sign a kept copy. Have a confidentiality clause that forbids theft of patient information describing HIPAA violations and the requirement of the practice to pursue those who violate this clause. A common example is the aesthetician employee who leaves for another job and takes all of your patient data to the next job. HIPAA requires you to protect such data and make attempts to retrieve it.

Internet and “blog” defamation law

The internet has dramatically influenced the practice of plastic surgery. Patients e-mail us from multiple states and seek information about care. It seems that patients share their

experiences on many of the social networks. Generally, the internet can bring us additional exposure and patients, while adding significant risk and potential problems. Some basic guidelines concerning e-mails are not to answer out-of-state inquiries with any specificity that the prospective patient can rely on. Failure to follow this guideline may expose you to practicing in the state in which you have no medical license – a crime. This only applies to prospective patients with whom you have not yet entered into a doctor–patient relationship. The practice should develop generic answers concerning basic information to respond to the out-of-state resident. It is usually recommended to include a disclaimer, e.g., if your symptoms and condition worsen you should seek help immediately in your community. The ongoing correspondence between the practice and the patient should be copied and recorded in the patient's chart. Telephone texting should have a similar documentation in the patient's file. Much of ongoing communication today involves internet messaging and it behooves the practice to establish policies which make such communication a necessary part of the medical record.

Many practices wish to enter the social networking community such as on Facebook or Twitter, establishing blogs and plastic surgery updates. One has to be very careful not to violate patient confidentiality by disclosing private information about procedures. One has to take care and not even mention what procedure you are doing on a specific day, as friends of the patient who might believe that day is reserved for their friend are now aware of the specifics about the procedure, which is a violation. One way around such exposure is to utilize generic procedures that are not specifically tied to a given day and include patient safety issues, general patient instructions, and current trends of plastic surgery. The practice must maintain a high level of professionalism complying with the HIPAA and other privacy issues. The use of photographs for commercial education and internet website usage require a specific written consent acknowledging their use. This is separate from the general photography consent considered as a part of diagnosis and treatment. The same considerations are given for office photographs, books, and references displayed to other patients.

A recent troubling trend is blogging by patients against the practice. A patient may have a perceived problem and begins to write on a website or a blogging page their interpretation of the negative. This is clearly one-sided and may in fact not be accurate. Despite this, the practice cannot respond, due to the HIPAA, without a specific written authorization. This one-sided attack poses great concern. There are attempts to control patients' speech through copyright law, but many believe this to be either unethical or restrictive. It may be suggested to develop a non-patient-specific practice blog outlining complications, noncompliance, and high risk procedures, as a balance to these attacks. The first inclination would be to attack the blogger legally, however First Amendment speech permits such opinions. The attacker who creates a fake website mimicking the practice is confusing and misrepresenting to the public, and may be subject to a lawsuit if you can identify and find them. Another suggestion is to utilize the internet search engines to place their blogging page on the second or third internet page, thereby reducing visibility. This will often lead to "games" where each attempts to manipulate the other, resulting in an extortion demand for money to

remove the blog. These actions by disgruntled patients have damaged many practices and threatened more. Attempts are being made to better control blogging sources in an effort to make this more fair and balanced.

Basic actions of a malpractice lawsuit (a guide)

There are many stages of a malpractice lawsuit. They include notice, discovery, pretrial motions, trial, and aftermath. Notice of the intent to file a lawsuit is controlled by each state with a required timely response by the physician or practice. Notice is usually provided certified for by a delivery service and must be taken seriously. As soon as notice is received, secure the medical records, and notify your malpractice carrier. Fight the urge to add to the medical record or alter it in any way. Obtain copies of the medical record from hospital facilities as well as your own office record. It may be wise at this point in time to ask employees as well as yourself to write a recollection of the patient's care and treatment with key words used prior to such writing, on advice of counsel and on anticipation of litigation. A life of a lawsuit may be over five years, and remembrances get lost over time as well as employees leaving. It is therefore suggested that, "on advice of counsel", each employee and physician in contact with the plaintiff write what they remember and keep these writings separate from the medical record. Keep these writings privileged and available only as an attorney–client work product, which the other side should not obtain. Keep these recollections separate from the medical record and under lock and key. There will be requests for medical records from the plaintiff and your malpractice carrier. You should have meetings with your carrier's agent and the assigned law firm. Usually notice is not the actual lawsuit but the intent to file a lawsuit should a settlement not be reached. Your carrier, attorney and you will discuss the case in depth evaluating the facts, standards of care, and defensibility. Once a lawsuit is filed, your team will develop an answer within the timed requirement and the process begins. Follow your hospital and facility by-laws, which might require notification of such a lawsuit.

The next stage is discovery. Discovery includes responding to written questions called interrogatories, and depositions to record testimony for future use. This process may take a number of years. You should remember to never respond to any such request without your attorney's input. You will have noticed your deposition well in advance and utilize the time to prepare at length with your attorney. All parts of discovery, such as depositions, require advance written notice of time and place. This allows one to prepare, collect information from the record, and seek consultation with legal counsel before actually providing the deposition. I would recommend you prepare with a senior attorney rather than the most junior associate. While you are quite comfortable in the operating room, the attorney is more comfortable taking your deposition. You must prepare by expecting certain questions, disclosing all concerns to your attorney, and understanding the process of the deposition. Once all the facts are gathered, a trial date is scheduled – make sure to block your calendar and devote the appropriate amounts of time for preparation. The pretrial stage includes demands from each side for exclusions,

expert testimony, and other concerns about your case. Frequently, arbitration or mediation is recommended by the court. A failure to reach settlement brings the trial date to schedule. The trial itself may take 1–2 weeks, depending on the complexity of the case and the court's schedule. You should plan on being there every day, following the advice of your counsel, being extremely respectful of the process and visibly concerned and gracious. The defense has two experts, while usually the plaintiff only one. You are your case's best expert and an additional expert is hired. Work with the expert and your attorney to win your case. It may be wise to travel with your attorney when taking the deposition of the plaintiff's expert as you may provide valuable on-site information to assist in their deposition. You will not be reimbursed for such travel, but the value to your case may far exceed your expenses. The last stage may involve appeals and other judicial and legal maneuvering, pending the outcome of the trial.

Aesthetic practice liabilities

The aesthetic plastic surgery practice has specific risks inherent to this area. Patient expectations are paramount to achieving desired goals and limiting risk. A disturbing trend is the lack of patient accountability combined with an unrealistic set of goals. It appears that any inherent risk or complication generates a legal concern even if fully disclosed in an informed consent document. More than ever, patient selection and appropriateness of procedure is important. Patients often demand certain procedures and the practice should be careful to assure the proposed procedure is an appropriate fit for this specific patient. Many believe it safer to create a more specific informed consent document listing the additional risks of such patient demands. The problem with this is that you may create additional risks by outlining such in a consent document. The ultimate responsibility of patient acceptance is yours and no document will protect you against an inappropriate decision. Smoking continues to be a major source of liability, as it affects healing as well as scarring and overall recovery. Adding additional risks to the consent is a good example of not avoiding liability where a better choice would have been not to accept the patient. Trends toward more mini procedures, while desirable for the patient, may not achieve the desired goals. Breast surgery continues to be the lead of malpractice claims, with augment mastopexy the majority. Any delay in healing, poor scar, or shape often leads to a lawsuit. Other trends concern where the surgery occurs, as questions arise after lengthy surgery in an outpatient setting. The balance between appropriate procedures, facility and anesthesia versus cost continues to be an issue.

Cosmetic medicine has assumed a lead in number of procedures performed and must follow general guidelines for risk prevention. Each skincare treatment, toxin injection, and filler injection should have a consent document. Additional concerns about who provides the treatment should follow state law, be it the medical board of the state, nursing board of the state, or skincare aesthetician governing body of the state in question. Establish patient care guidelines and follow them throughout the practice. An example might be: a patient for IPL treatment who, despite being told not to get a suntan, comes in for a treatment with a tan. It is wise not to treat the patient, despite their anger or demands. It is suggested that

you see prospective patients at least twice preoperatively allowing time for questions and procedure refinement. Include financial agreement discussions about costs of the proposed procedure as well as future costs, especially if a complication occurs. Develop a team to both address the patient's needs as well as discuss appropriate procedures and treatment plan. Recognize today's social pressures and media influences to present options to the patient that are realistic for the physician to achieve their goals. Try and avoid gimmicks and competing with unrealistic choices to keep the patient in your practice.

Managed care liabilities

The distance between aesthetic surgery and managed care/reconstructive surgery is narrowing. Patients have as many demands and unrealistic expectations for reconstructive surgery as they may exhibit in aesthetic surgery. The practice should present realistic options and procedures to the patient and after a clear understanding and acceptance, proceed with treatment. Additional concerns may arise with managed care coverage, and these should be addressed with the patient with good documentation. Your authorization letter should be honest, complete, and represent the facts and why treatment is medically necessary and appropriate. As you know, it is not uncommon to receive a denial, but remain a patient advocate and appeal as appropriate and necessary. The practice should be careful in not discussing fees with competitors, as this could violate antitrust laws. If you provide service through an emergency room, and not on the patient's managed-care panel, attempt to see the patient postoperatively without charge and document their satisfactory progress.

The Affordable Care Act creates liability on the physician even though a PA or nurse practitioner may actually see the patient. If the expected volume of patients become involved in care, physician interaction for all patients becomes impossible. There will be delays in treatment as well as rationing of care. It behooves the physician to establish criteria for treatment and a direct supervision method to assure appropriate care for all seen under the physician's umbrella.⁵⁻⁷

Liability carrier's issues

The choice of carrier providing your malpractice insurance is a critical one. Inquire as to their financial stability, track record, coverage inclusions, claims made or occurrence type, opportunity for purchase of a tail, and contractual decisions about settling claims. There is an increase in state board complaints and ask whether representation is included in their coverage. Check on which law firms represent physicians through the carrier and how responsive they are to the physician. It is not only the premium that should affect your choice. Many physicians have paid a very low premium only to subsequently find out the company is bankrupt and they have no coverage at all. There are carriers common to plastic surgery that are active within our societies and understand the nuances of a plastic surgical practice. Determine your limits of coverage based on your practice, hospital privilege, and risks and exposures. The level should be appropriate to maintain hospital and facility privileges, yet not excessive, helping to make

you a target. Evaluate companies that encourage discussion about problem patients while not considering each inquiry a claim. Look at their rating and past record in a plastic surgery arena.

Legal issues in physician partnerships

A higher percentage of physicians are associating with partners than in the past. It becomes important to understand the legal implications of such arrangements. There are many types of associations from full partnerships, office-sharing arrangements, limited liability partnerships, single specialty groups, and multi-specialty groups. One considering such an association should seek input from their accountant, attorney, estate financial planner, family, and compliance with their business plan. Spend considerable time with the individual you seek to join or associate with. It is amazing how often what started as a great idea of like minds ends up with exasperation in being so different in goals and style. Make sure you complement each other, and can retain some of your autonomy and individualism, important to a plastic surgery mindset.

Whatever format you choose, establish a communication mechanism, as well as a conflict resolution format. The best of intentions can rapidly go downhill without continuing to “make it work”. Have legal counsel work with your business plan to make it equitable and yet protective to both/all parties. All aspects of the arrangement must be considered, especially financial, and termination issues. The agreement is a binding contract and must reflect *all* considerations agreed upon. There should be no verbal or handshake addendums that are not included within the pages of the agreement.

Issues to consider and resolve are:

1. Ownership – office, equipment, other investments, and the right to make decisions about new and past expenditures
2. Duration of the agreement, including renewals, termination, and adjustments
3. Duties and expectations of each party should be carefully defined and described
4. Financial allocation of expenses – fixed (rent, employees, leases, personal expenses, e.g., pager, etc.), variables based on collections (medical supplies, office supplies, etc.)
5. Ethics – defining standards (ASPS, ACS, state board, federal), malpractice requirements
6. Termination process – who gets what, staff issues, costs involved, e.g., to copy records, etc.
7. Hold harmless clause – adding staff and physicians’ decisions, management of office
8. Accounts receivables (always difficult) – possibly a trust established by senior associate keeping funds collected by junior associate, but in name of junior associate, only released when agreement and liabilities are resolved
9. Financial considerations – bonuses, salary, advances, etc.
10. Confidentiality clause
11. Marketing; advertising
12. Ownership of telephone number, name, etc.
13. Restrictive covenants – can and will be enforced as long as “reasonable” as to time, description, and distance. So,

a restriction for the practice of medicine for a period of 5 years in the entire city will probably not be enforced. However, a restriction for the practice of plastic surgery for a period of 1 year within 5 miles of every office location currently used probably will be enforceable. Another option is to consider a “liquidated damages clause”. This acknowledges the difficulty in enforcing such restrictive covenants, and in advance, arrives at a money settlement (e.g., \$150,000) that the leaving doctor must pay the other doctor for breaching restrictive covenants. This amount may be withdrawn from accounts receivables due to the leaving doctor or other arrangements that are enforceable.

There are many more considerations necessary for a successful association, despite the legal structure. The most important is perceived fairness and ongoing attempts to keep it positive, efficient, and responsive to the many changes and challenges affecting the plastic surgery practice.

Patient selection

Patient selection has become the most important part of risk protection as well as practice building. There is a disturbing trend of less accountability in the patient and an approaching “must be perfect” expectation for the practice. Lawsuits have been filed by patients who develop a known inherent risk of a procedure, despite having good documentation about such risks in advance. Lawsuits have been filed even with poor patient compliance, even when discussed in advance of how important this is. It approaches a mindset that any inherent risk or complication must have been the result of “something done wrong”.

The key to limiting this is to choose patients you feel you can trust and those for whom you can realistically reach their expectations. It is wise to see the patient more than once pre-treatment to assess their goals and expectations, as well as how they interact with you and your staff. In tough economic times, it is difficult to say “no” to a patient, but “no” is much preferable to defending a malpractice lawsuit. Be realistic in approaching your choices of procedures. Patients are becoming more specific-procedure driven, rather than issue driven. They might come in asking for a facelift, when in fact other choices might be more beneficial and appropriate. We should educate them and understand we are responsible for the choices made, not the patient. We are the experienced physicians and our role is to protect and guide the patient, sometimes protecting them from themselves. It is not appropriate to grant the patient’s desires unless they are appropriate and achievable. There is a difficult defense in a malpractice suit when the defendant physician states “the patient wanted this procedure and signed all the informed consent documents indicating greater risk”. The physician has the task of approving procedures, not the patient. The patient cannot appropriately consent to an inappropriate procedure. The surgeon should have either rejected accepting the patient or suggested an appropriate procedure. There is distinct added liability from not following this principle.

Dr Mark Gorney developed a “GorneyGram” that helps physicians assess realistic goals of the patient (Fig. 6.1). It balances the deformity present against the effect such a

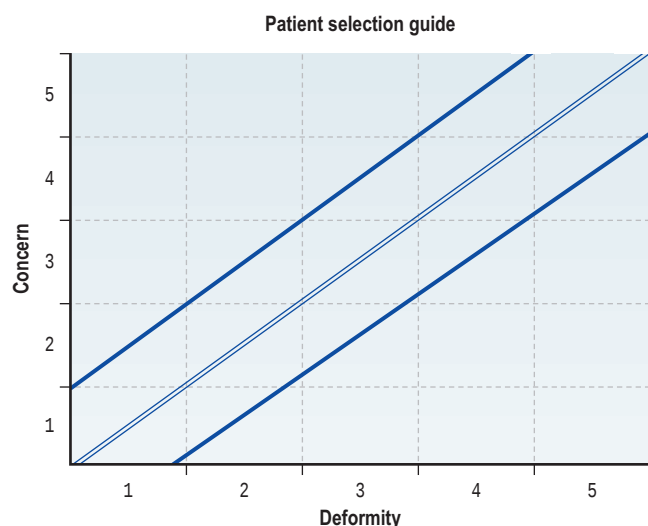


Fig. 6.1 Dr. Mark Gorney developed a “GorneyGram” that helps physicians assess realistic goals of the patient.

deformity has on the patient. For example, Quasimodo, the hunchback of Notre Dame, seeks contour corrective surgery. He states anything you can do to improve things would be great. Quasimodo would be on the bottom right of the GorneyGram; a good place to be. Another patient with a minimal small 1 cm scar on her lower cheek from chickenpox cannot leave the house without covering it to extreme. This patient is in the upper left area of the GorneyGram; a most dangerous place. Likely, nothing you can do will help the patient to her acceptable level. There should be an assessment of all patients to see where they lie on this scale. Some areas will change over time, but it is amazing how accurate this is overall in helping to define which patients are better candidates for your care.

Electronic medical records

The Affordable Care Act has increased the requirements to utilize electronic health records (EHR), but with an increase in patient complaints and claims. The necessity of documenting on a computer or tablet can remove the face-to-face interpersonal contact with the patient. It has been well accepted that patients are less likely to bring a medical negligence claim against a physician they like. Often the doctor’s mind is focused on a computer and not on the patient, becoming an obstacle in the doctor–patient relationship. It is suggested that a routine is developed in which a direct interpersonal discussion with the patient begins, and only after a relationship is established will after an apology in needing to document this examination and treatment the doctor focus on appropriate documentation. This new paradigm is a learned behavior and some practice may help achieve the proper balance between correct documentation and a personal visit. The second area of risk associated with EHR is the “smart text” developed for each specialty to facilitate data entry and speed up the required time. The default data developed by the programmer, usually along with the physician, must be checked to assure it is correct. It might be easier to utilize

default smart text phrases but, if incorrect, this sets up the physician for liability. The physician exam with “No masses seen” as a default text must reflect the reality that no masses were seen. It is suggested that the smart texts are reviewed for accuracy and inclusion. Once signed, you verify the correctness of the medical record. If such entry is incorrect or false, your credibility in the courtroom is questionable. The third area of EHR concern relates to privacy issues. An aesthetic patient seeks a breast augmentation and liposuction. She demands that this surgery remain private and is not to be shared with anyone. No insurance is involved and therefore no fraud issues arise. However, in a health system all the data from her surgery is in the EHR for the next physician to observe. I am not aware of a mechanism to restrict such data, preventing viewing by future physicians unless the patient approves or it is necessary for care. I would explain this to the patient. Even though they seek confidentiality, their EHR record will include all surgeries they have experienced. HIPAA should prevent subsequent healthcare providers from disseminating such information, but patients have become angry at their plastic surgeon when a family practice physician discusses their breast augmentation and the patient believes you were told to keep it private.

Summary

There are many legal interactions and risks within a plastic surgical practice. One should be aware of these risks and develop standards of protecting the patient, practice, and physician. I would suggest attempting to keep up with the changing medico-legal environment by attending risk courses; explore state medical board rule changes, and the plastic surgery societies’ panels. Establish relationships within the legal community as your practice grows. This will become a useful resource for questions that arise and have a positive impact on the medical malpractice arena. Understanding all of the above is important, but the most important risk protection is appropriate patient selection. Choose patients you like and feel you can trust, and develop a relationship. Match the chosen procedure with their expectations and follow them as you would want to be seen if you were the patient. Develop a team that reflects your attitude and caring for the patient.

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Digital imaging in plastic surgery

Daniel Z. Liu and Brian M. Kinney

Access video lecture content for this chapter online at expertconsult.com 

SYNOPSIS

- Photography is not only useful, documentary, collaborative, didactic, medical-legal, a research tool and even promotional – it is standard of care and a *sine qua non* for proper practice in plastic surgery.
- Our specialty is highly visual and relies on accurate representation of form, as well as function, to diagnose, plan, treat, evaluate, and track patient surgical outcomes.
- The photographic record contains much more information than can easily be documented in words, including color, tone, texture, shape, vascularity, bulk, spatial relationships of anatomic structures, global aesthetics, aging, and historical changes, to name only a few.
- The value of images increases with time.
- Technological advances in videography and three-dimensional surface imaging in plastic surgery may improve communication, education, and patient satisfaction.

Purpose

The first principle of photography as a medical record is to document the pre- and postoperative condition of the patient, serving as an accompaniment and function analogous to radiography. Preoperatively, the record is a guide in evaluating the patient's condition, highlighting relationships of the anatomy, and demonstrating aspects of physiologic function for tissues like the nose, eyes, mouth, and hand. Postoperatively, images record changes for patient teaching, self-evaluation for retrospective review, and assessment of results *vis-à-vis* planned outcome. Intraoperative imaging may feature key aspects of the surgical procedure.

Much of plastic surgery rests in an unusual setting in medicine. The core and history is reconstructive in nature, largely born from efforts to rebuild injuries sustained by First World War soldiers. Whether reconstructive or aesthetic, its essence is to restore form and function, and today, a great portion is neither urgent nor critical to immediate health. Instead, much is elective and focused on quality of life,

especially in the aesthetic arena. Reviewing photographs with a patient may transform the preoperative planning from an interaction tilted one way from the doctor *to* the patient. Instead, the effort may be collaborative and consultative, an interaction between the doctor *and* the patient.^{1,2} Various scenarios can be examined and evaluated with digital imaging, modeling and morphing. Care must be taken when showing potential postoperative results, to avoid the implication of an implied or guaranteed result.³ One popular software program (Mirror Image)⁴ contains an important default disclaimer, "Simulation only: Actual results may differ."

The didactic nature of medical photography cannot be underestimated. Decades ago, sketches were used, followed by black and white photography, color transparencies and film, with the modern progression to digital images in the last 20 years. For all practical purposes, analog photography is a niche market, and digital imaging reigns supreme. Between the consultation and the operative procedure, planning requires good recall and representation of the anatomy. The images serve to refresh the memory of the surgeon. In addition, it is critical for patients to understand excesses or deficiencies of tissues, issues of symmetry.³ Features of their anatomy may facilitate or hinder surgical planning, influence choices in surgical approach, affect risks of complications, compromise or augment patient satisfaction. Patient teaching requires proper photographic representation of the preoperative condition and explanation of the changes achieved with surgical intervention. The evolution of a surgical practice can be tracked most easily over a period of years through systematic inspection of imaging of the patients' condition through the course of their diseases or conditions. A particularly common phenomenon is for a patient to not recall how they looked before surgery when critically viewing the postoperative result. Occasionally in reconstructive procedures and more often in aesthetic ones, the patient's psychological "set point" is re-established at their current condition, and the desire for further enhancement leaves them with falsely elevated expectations. Photos are indispensable in this setting and may provide reassurance that goals have been reached.

Maintaining proper images and systematically evaluating them postoperatively can only improve awareness of surgical choices and outcomes. Properly preserved analog images may last decades with original fidelity and 100 years or more with mild degradation. Digital images may not last much longer. Challenges in the evolution of technology lead to viewing problems (incompatibilities in hardware), scrambling issues (changes in compression algorithms), inter-relation limitations (expired webpages or hyperlinks), custodial problems (where the data resides), translation issues (how to read old storage with new technology) to name a few. If digital concerns are solved, images could last centuries or more.⁵ Building a digital database and engaging in periodic data mining is a core component of self-improvement in clinical care. The advent of digital photography eliminates concerns about lack of space, difficulties in storage like degradation of image quality, the ability to compare past and present results over large series and related issues. However, they are subject to their own vagaries. Old retrieval technologies (floppy disks, CDs, etc.) are subject to catastrophic failure. For example, a scratch on a transparency may slightly degrade the quality of the image, while the same event in a digital image may make it unreadable. Digital images must be backed up, and the methodologies rapidly change necessitating continual hardware upgrades. The best storage methods have changed 5–10 times in the last 20 years from floppy disk to magneto-optical disks, magnetic tape back-up, compact discs (CDs), digital video discs (DVDs), USB flash drives, portable hard drives, network attached storage drives, and more recently, “in the cloud” at a remote data storage center on the internet. Much like the evolving standards in business and research regarding storage of e-mail and digital documents for potential legal cases, our *de facto* standards dictate that photographs must be preserved, organized, properly referenced and identified, while easily retrievable.

Informed consent is a key part of medical record-keeping, and photography is essential to proper medical records. Almost every patient understands that photographs are part of the medical records. In fact, many insist on seeing “before and after” examples in their initial consultation, the best time to establish the necessity of accurate documentation. Some patients have a strong need for privacy; however, most surgeons will refuse to operate on a patient who refuses medical photography. Patients understand they have control and options on how their pictures will be used. Some practices allow only internal records in their private chart, others may permit sharing with other patients in consultation without identifying data, and some are comfortable with unrestricted use on the internet, in print, and television advertising. A thorough, detailed consent form specifically for the use of images is necessary for a proper medico-legal record.¹ Consent forms from the American Society of Plastic Surgeons are available for member surgeons.⁶ Photography’s utility as a research and interpretative tool in our field is without question.⁷ Comparison of how our journals have progressed from the first decade of the 20th to the 21st century shows that our journals have gone from black and white to color photographs, to online digital images in low and high resolution, to online video. Three-dimensional simulations that allow a “fly through” of the anatomy have been available for several years. Information density in images is an order of magnitude greater than the written word. With decreasing costs in the digital era,

increasing use of imaging improves learning and documentation. In coming years, widespread use of artificial intelligence for image processing will likely allow for digital data mining of the image content itself. This would be a major advancement beyond assigning database attributes to digital files like age, preoperative and postoperative photograph dates, type of procedure, etc. Instead, we may begin to see digital reference to quality of outcomes, conditions of anatomy on validated grading scales, etc. Even now, consumer digital cameras and photography software have “face finders,” automated red-eye reduction and similar tools. Professional systems have capabilities like automatic pore evaluation on the skin and cell counters for microscopic work. One could imagine many future potential applications like automatic color detection, evaluation of cutaneous vascularity, flap perfusion and others.

Since the mass “migration” to the internet by the general population, the public has turned online to research plastic surgery, compare results, investigate complications, nurture special interest groups and procedures, and engage in promotion and marketing. There are many egregious examples of excess, manipulation and deception; however, there are even more beneficial opportunities for patient education, practice marketing, advocacy and public health outreach. In addition, surgeons often disregard photographic documentation standards of care.⁸

Standards in capturing images

Little has changed for the framing and composition of images since Morello *et al.*⁹ and Zarem,¹⁰ and many before them specified these aspects of photographic standards in plastic surgery. However, many other factors have evolved in the transition to the digital world.¹¹ Key principles must be followed.¹² Consistency in results is affected by numerous factors.^{7,9,10,12} Facial photographs are taken at the 35 mm camera 100 mm lens digital equivalent, while body images are taken at the 50 mm lens equivalent.¹³ Shadows should be avoided. Colors must be natural. Lighting should be unobtrusive and consistent. Standards must be obeyed.^{14,15}

Digital image characteristics

Many variables affect images, and many are in the control of the plastic surgeon. Parker *et al.*⁷ have documented four basic ways in which inconsistency is introduced into photography: (1) photographer-based; (2) publisher-based; (3) combined; and (4) patient-based. Category 1 in their scheme includes view (composition), background and zoom, which are generally consistent among journals. Publisher-based criteria, size and image labeling are less problematic. Combined criteria, color, brightness, contrast, and resolution vary in published journals. Category 4 criteria: clothing, accessory apparel, make-up, facial expression, and hairstyle, are designated as patient-based, but are substantially under the control of the photographer. A dark-colored “collar” drape can be used over the shoulders for facial photographs. Accessory apparel should be removed, as make-up, false eyelashes, and similar accoutrements of fashion may interfere. Hairstyle can be mitigated by using standardized hairbands or ties. Patients can be coached to maintain neutral facial expression.

Galdino categorizes factors into direct and indirect.^{11,12} Direct variables include lens, viewfinder, digital chip, resolution,

Key principles

- The same camera and photographer should be used. Changing a digital camera (and therefore the color and white balance) essentially alters the pixel resolution, photonic sensitivity and hardware image processing.
- Shutter speed and aperture must remain the same. Positioning of the patient and photographer in the room should not vary.
- Guide marks on the floor may be required; flash equipment and lighting should not vary.
- Adequate lighting is essential. Shutter speed should be at 1/60 of a second or faster.
- On digital cameras, keep the magnification factor comparable with a 35 mm camera 100 mm lens for essentially all images except full body views, where a view comparable to a 50 mm lens may be used.
- Focus by moving the camera closer or farther from the patient and note the position of the mechanized zoom lens barrel in relation to the camera body.
- Do not change the white balance, and keep it in sync with the lighting used (often flash or fluorescent) on a medium blue background.
- While modern cameras often contain 16 megapixels or more, generally more than 6 megapixels are not required.
- Space for digital images is not an issue in this era of terabyte hard drives, and the speed is easily adequate for rapid access of data.
- More images than will likely be used in a career can be stored on portable drives.

compression and software algorithms of the camera. Indirect are listed as lighting, metering, depth of field, color temperature of lighting and output method. Both categories are easily controlled by retaining consistent techniques from visit to visit (see [Key principles box](#)).

Background

Medium blue or 18% gray featureless backgrounds provide the best skin tones and affect exposure least. White or black backgrounds affect exposure on the most commonly used camera setting (matrix metering), so the mode must be changed to spot mode metered on the skin in the center of the field. However, the sharp contrast will not create a natural skin coloring. Standard blue towels used in surgery are close enough to ideal to be used without problems, but green surgical towels are not.

White balance

Accurate, lifelike color reproduction is dependent on neutrality, an equal distribution of colors in the white, gray and black in the image to ensure accuracy of hue. A color-balanced image contains all hues in equal proportions of illuminating white light. Unfortunately, different types of reference white points exist in various environments. Indoor scenes lit by incandescent lamps are distinctly different from daylight. Fluorescent lights come in various shades of blue. Operating room lighting is variable in color, temperature, angle, and distance from the

patient. The white balance adjustment attempts to capture neutral colors by compensating for these changes. Modern digital cameras have numerous settings like daylight, fluorescent 1 and 2 (or high and low), and auto white balance, among others. The auto white balance setting is often misled by the pulsations of overhead fluorescent lights and may produce variations from image to image. Flash lighting minimizes the effect of ambient light and forces the use of smaller aperture, lower ISO, and shorter exposures. Ideally, a multiple flash system in a dedicated photography studio is used to eliminate these problems in order to capture flesh tones consistently and accurately. Single on-camera flash is inadequate due to shadowing effects in all backgrounds except black.

Lens aperture and shutter speed

There is a delicate balance among aperture, lighting, and shutter speed. A narrow aperture (high F-stop) provides increased depth of field compared to a larger aperture. Too wide an aperture (low F-stop) allows for a shallow depth of field, which creates difficulty, for instance, in capturing simultaneous changes in the crow's feet area and the submentum. An F-stop of 16 or less should be used, with consistency maintained over pre- and postoperative settings. Skin with darker pigmentation may require a larger F-stop.

Shutter speed controls the amount of time that light is exposed to the image sensor. Increased shutter speed allows less light in, while decreased shutter speed results in blurry images with subject movement.

Composition and positioning

Full face

In the anterior–posterior (AP) view, the superior border of the head must be framed by a small amount of background, about 10% of the vertical height of the image or 2 cm above the vertex of the skull. The inferior border of the image should stop just below the suprasternal notch. The Frankfort horizontal plane connects the infraorbital rim to the tragus and is kept parallel to the floor. For the frontal view, the ears can be used to ensure proper positioning. In the lateral view, the patient's body and head should be facing 90° from the focal plane of the camera. The eyebrows should be superimposed. While some cropping of the occipital region is acceptable, in general, lateral views should include the full view. Oblique views should be taken at 45° and, in this view, the tip of the nose should protrude slightly beyond or rest just at the contour of the distal malar eminence. Five standard views are taken, an AP, two oblique and two lateral, right and left for each of the latter two ([Fig. 7.1](#)). When indicated, the malar eminence may be imaged, generally the bird's eye view is preferred over the worm's eye view, unless a particular feature of anatomy is involved.

Musculature should be relaxed in all photographs unless otherwise specified.

Eyes

The same five image views (anterior, two laterals and oblique views) are part of the basic set for the eyes. Close-up images of the eyes should include a small border of forehead skin above the eyebrows and extend inferiorly to the upper lip at the nasal spine. For the lateral and oblique views, positioning

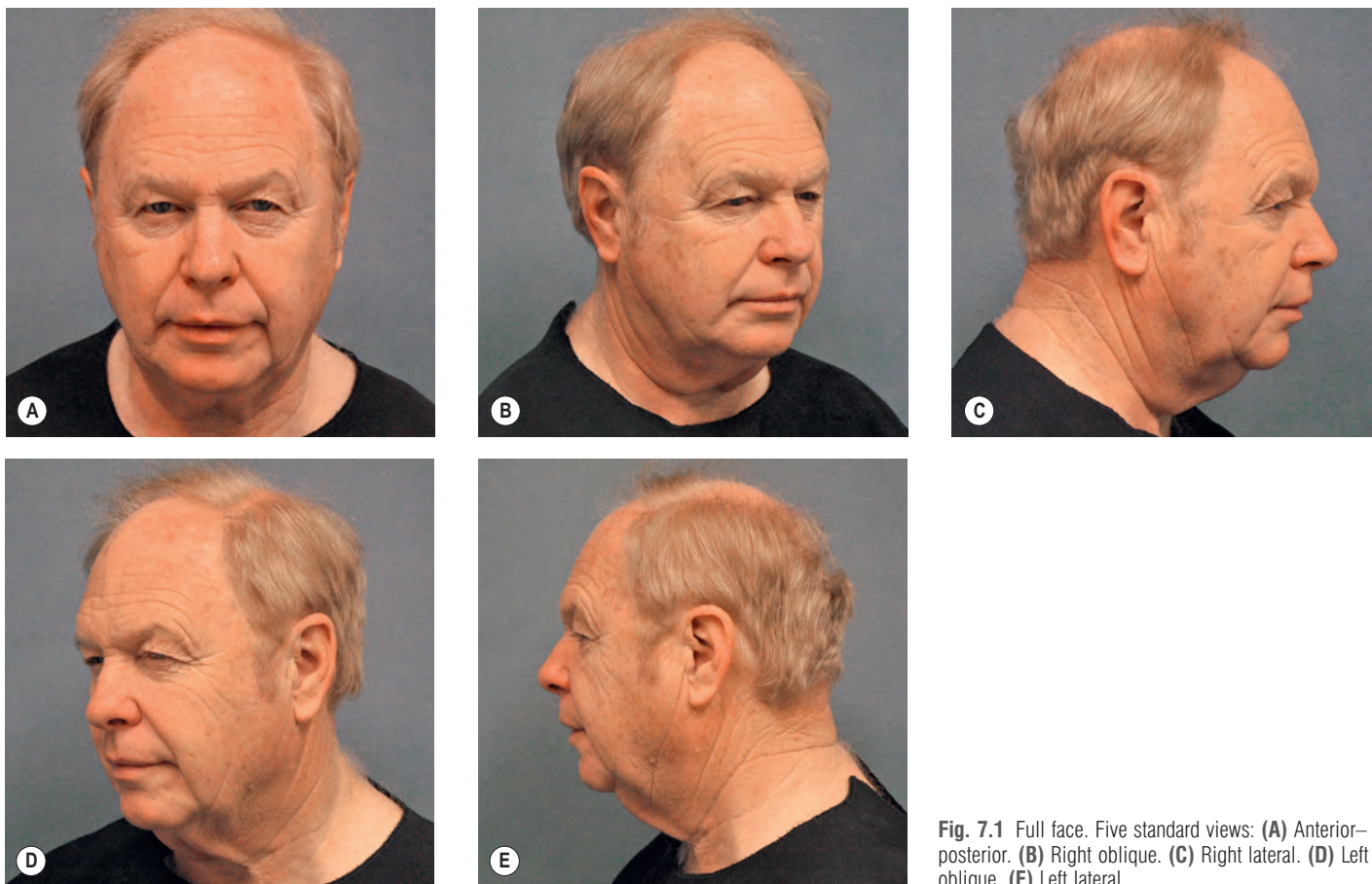


Fig. 7.1 Full face. Five standard views: (A) Anterior–posterior. (B) Right oblique. (C) Right lateral. (D) Left oblique. (E) Left lateral.

is similar to the views of the head honoring the superior and inferior borders herein. Additional views are essential and include the following at a minimum: (1) closed eye view to highlight the superior tarsal sulcus and fold, and (2) upward gaze to highlight inferior orbital fat pockets and the lower lid margin. A squinting view consists of open eyelids with contracting of the superior and inferior orbicularis oculi to feature the impact of muscle action on eyelid shape and function. Occasionally, a view with tightly-closed eyelids to highlight the orbital orbicularis, zygomaticus muscles and others is required for certain surgical procedures (Fig. 7.2).

Glabella

Images of the corrugator muscles may be taken at rest and on full contraction to document wrinkling on the validated four-part glabellar rhytid scale (Fig. 7.3). Full face images are often used; however, the superior border is best cut off at the location (or former location in baldness) of the anterior hairline and the inferior border is often positioned midway between the radix and the tip of the nose on a horizontal line through the lower margin of the malar eminence. The closer view provides more detail of pore size, eyebrow position and skin texture. Oblique and lateral views are generally not necessary.

Nose

The superior margin of the nasal view is essentially the same as for the eyes – just above the eyebrows. However, the

inferior margin is at the upper lip or between the closed lips. In addition to the five basic views, worm's eye view or chin-up view is included (Fig. 7.4). The superior and inferior borders are the anterior scalp line and the mentum, respectively. When muscular release at the dorsum or nasal spine is contemplated, dynamic pictures of contraction should be included.

Lips, nasolabial folds, and mentum

The superior border is on a line just above the nasal tip and includes the alar base, while the inferior border allows a small amount of background to show below the chin (Fig. 7.5). The lips should be slightly parted to detect features in the mucosal surfaces near the intersection of the upper and lower borders. When injections into vertical lip lines are performed, the pursed lip or orbicularis-contracted view is added. Additional views may include contraction of the mentum when toxins or soft-tissue fillers are part of the therapeutic intervention.

Dental occlusal views

When intraoral or two-jaw surgery is considered, dental occlusal views are required, and transparent cheek retractors must be utilized.

Ears

Adequate visualization of the ears requires that the hair must be retracted. Anterior and posterior views should include the

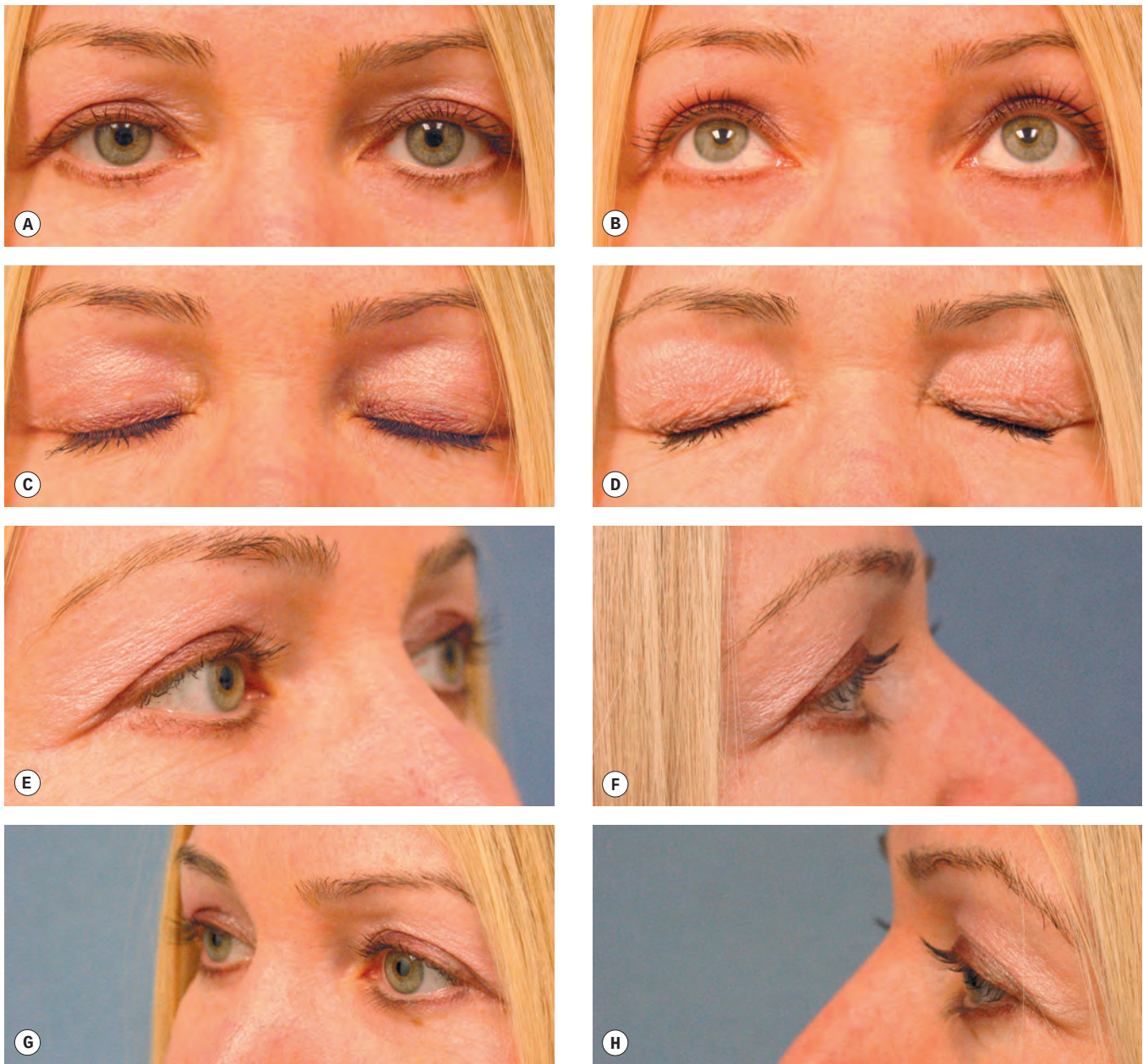


Fig. 7.2 Eyes. Standard views: **(A)** Anterior–posterior view. **(B)** Anterior–posterior view with upward gaze. **(C)** Anterior–posterior with eyes closed gently. **(D)** Anterior–posterior with eyes closed tightly. **(E)** Right oblique in forward gaze. **(F)** Right lateral in forward gaze. **(G)** Left oblique in forward gaze. **(H)** Left lateral in forward gaze.

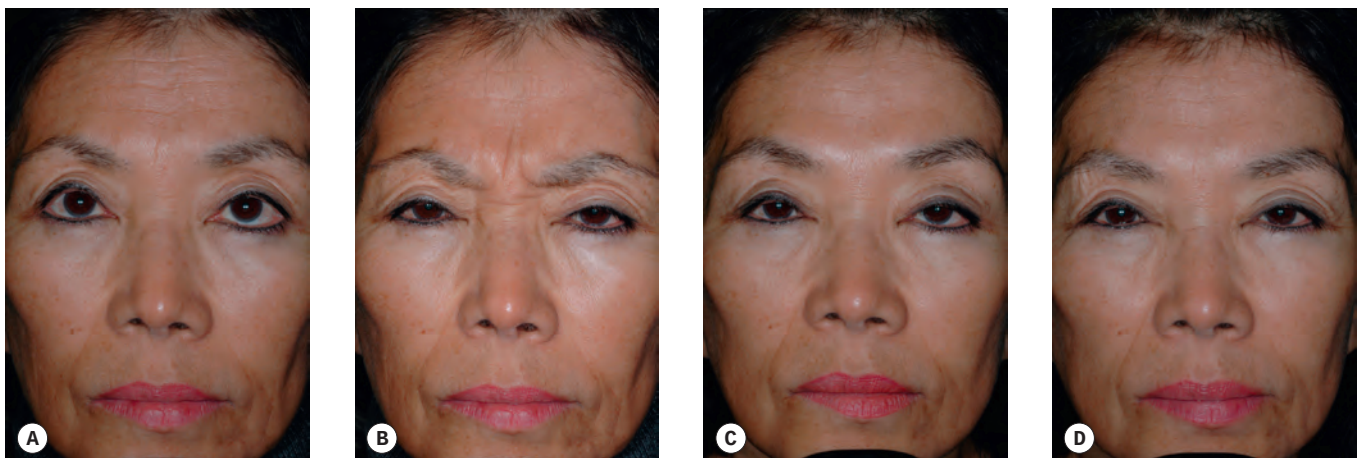


Fig. 7.3 Glabella. **(A)** Glabella relaxed. **(B)** Glabella contracted. **(C)** Glabella post relaxed. **(D)** Glabella post contracted.

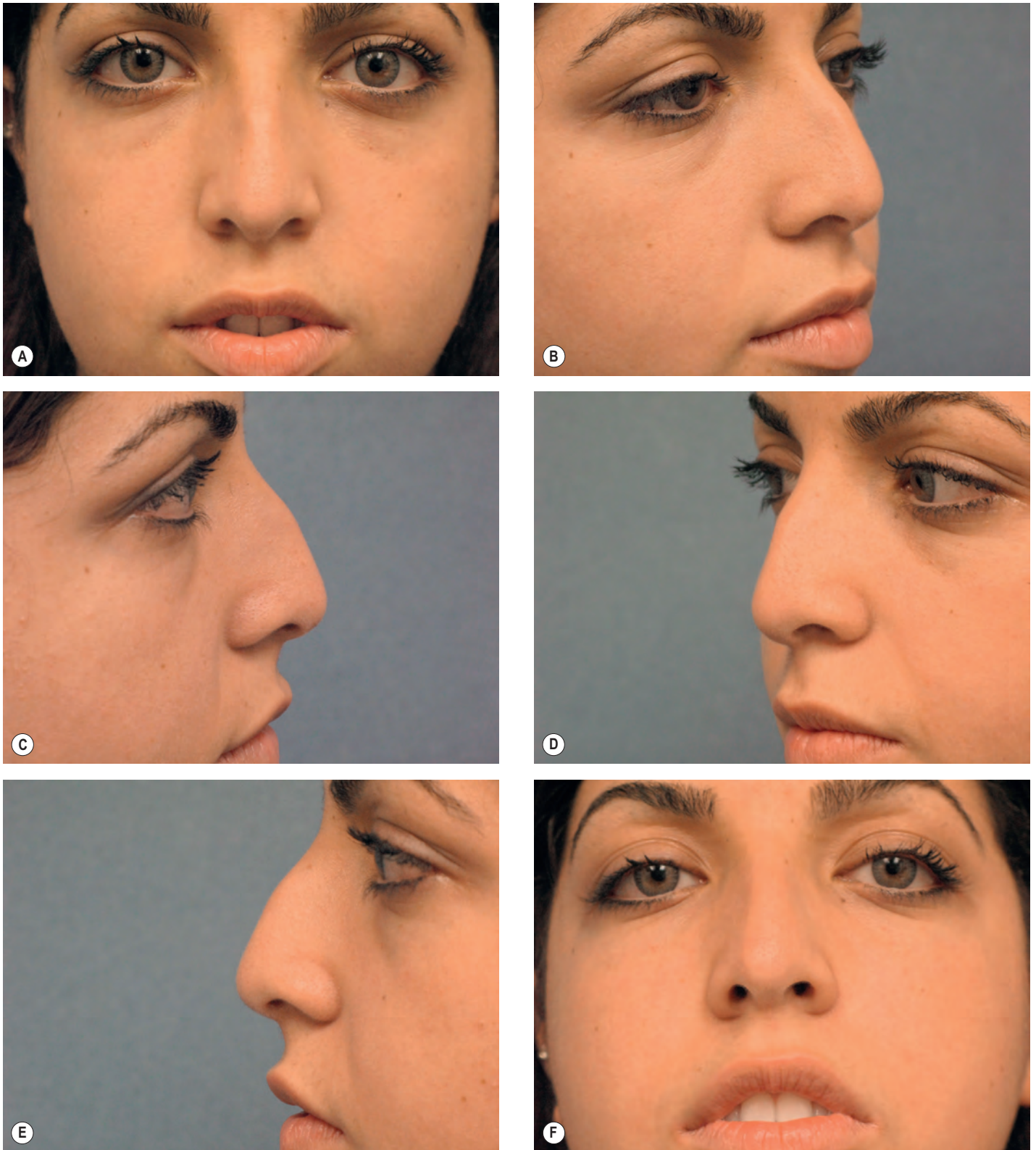


Fig. 7.4 Nose. Standard views: (A) Anterior–posterior. (B) Right oblique. (C) Right lateral. (D) Left oblique. (E) Left lateral. (F) Tilted head view.

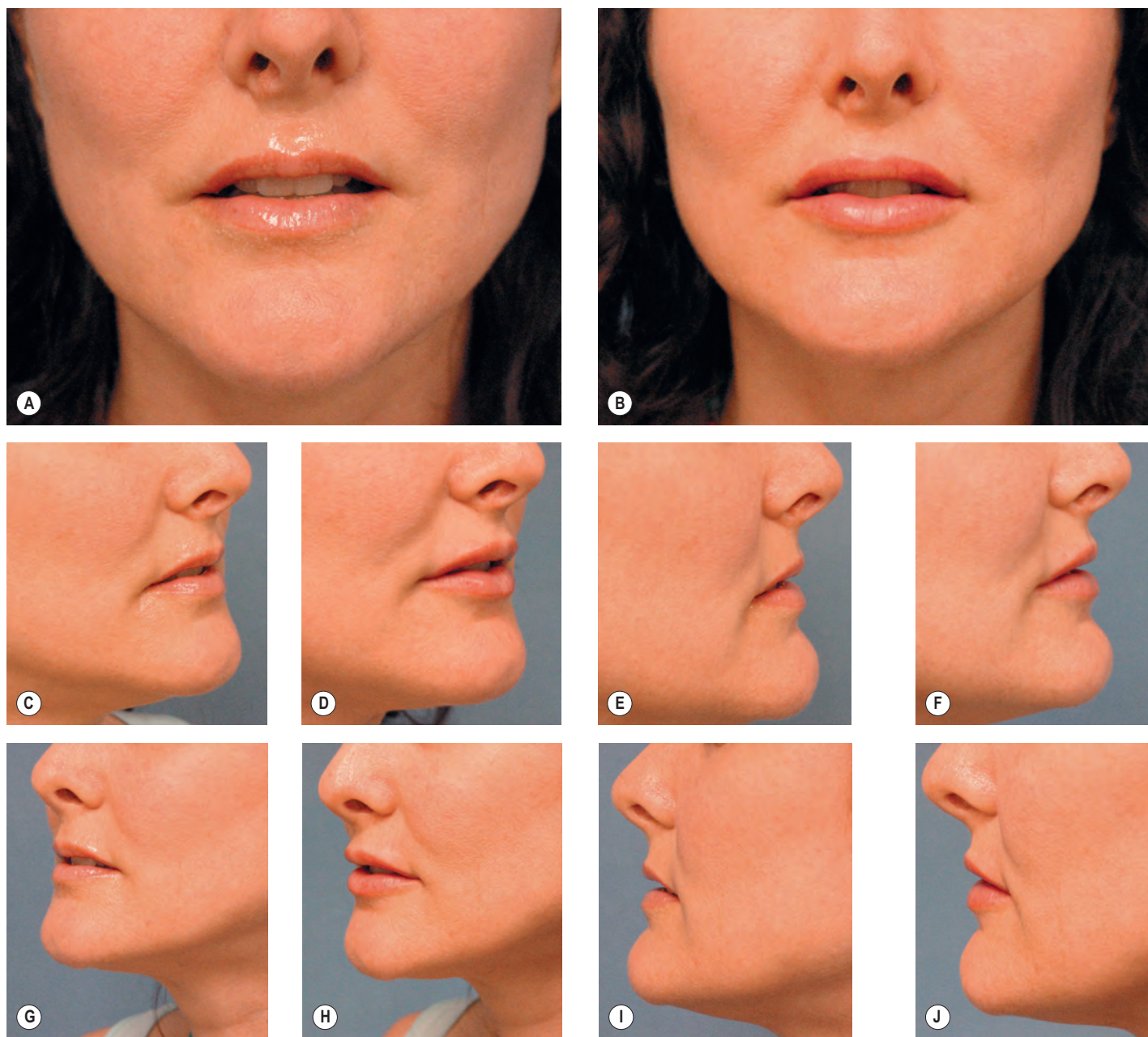


Fig. 7.5 Lips, nasolabial folds and mentum. AP view: (A) Pre- and (B) post-procedure. Right oblique: (C) Pre- and (D) post-procedure. Right lateral: (E) Pre- and (F) post-procedure. Left oblique: (G) Pre- and (H) post-procedure. Left lateral: (I) Pre- and (J) post-procedure.

full head and supplemental mid-range views should extend from the upper neck to above the occipital ridge to bring the ear more fully into the image. Lateral images should include close-up composition with the vertical height roughly twice the height of the ear itself.

Chest and breast

Variations in the configuration of the trunk dictate that the principle of bordering the image based on regional anatomy is critical in these images (Fig. 7.6). Vertical borders should range from above the suprasternal notch in the lower third of the neck to below the mid-costal margins. Patients should be disrobed above the waist, and all visible jewelry must be

removed. There are three basic variations in arm positioning on the lateral view of the breast: (1) arms at side; (2) arms on hips; and (3) arms behind the lower back. The most common, in the author's experience, is the former. Oblique views may be taken in positions 1 and 2 above, while occasionally AP views are taken with arms above the head. Dynamic pectoralis animation deformities may be highlighted on AP views with hands pushing against the hips.

Lower trunk, abdomen, and buttocks

The five standard views are supplemented with a posterior view (Figs. 7.7, 7.8). When the buttocks are the focus of the image, no panties are used. It is essential to use disposable,

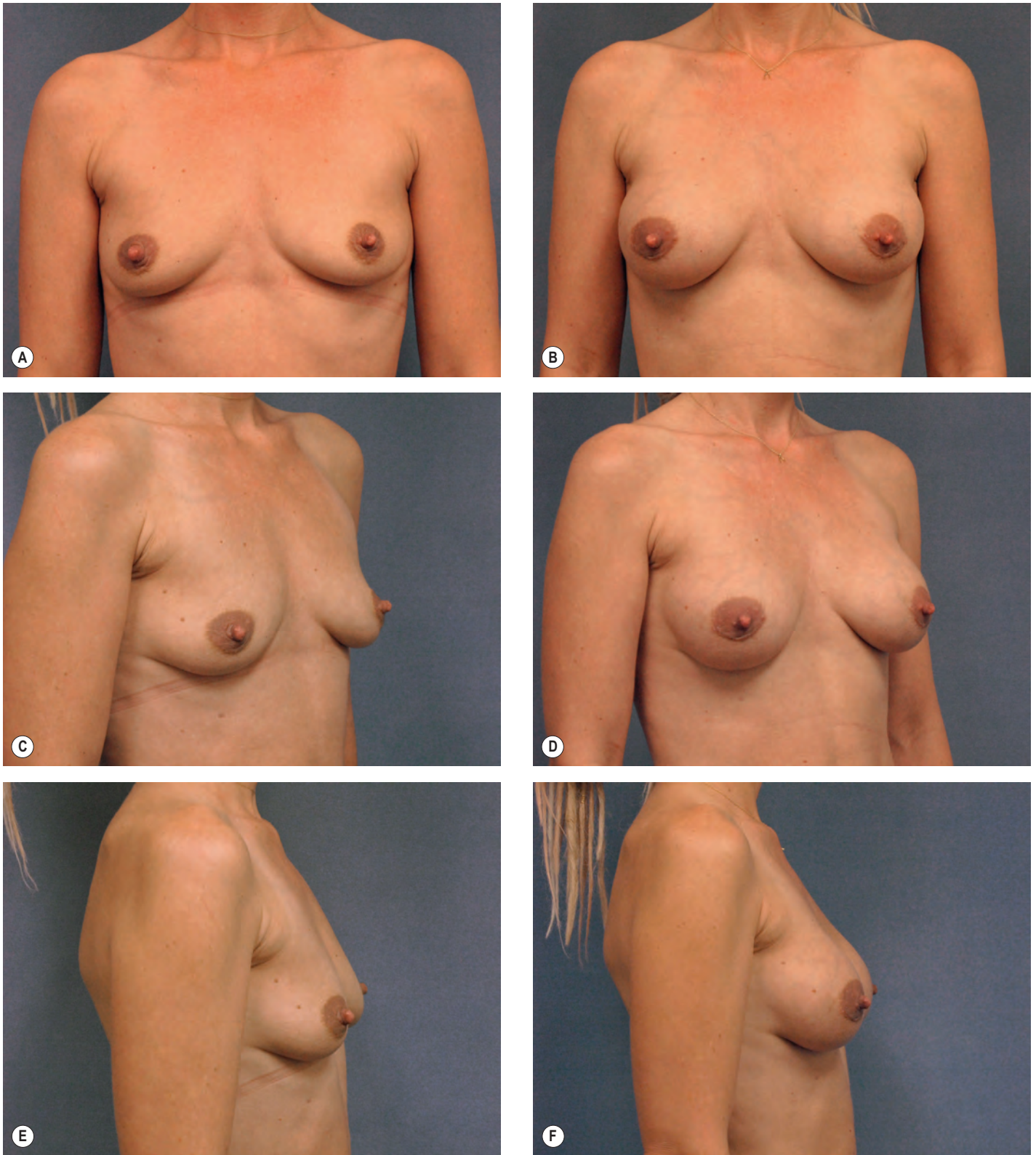


Fig. 7.6 Chest and breast. AP view: (A) Pre- and (B) post-procedure. Right oblique: (C) Pre- and (D) post-procedure. Right lateral: (E) Pre- and (F) post-procedure.

Continued

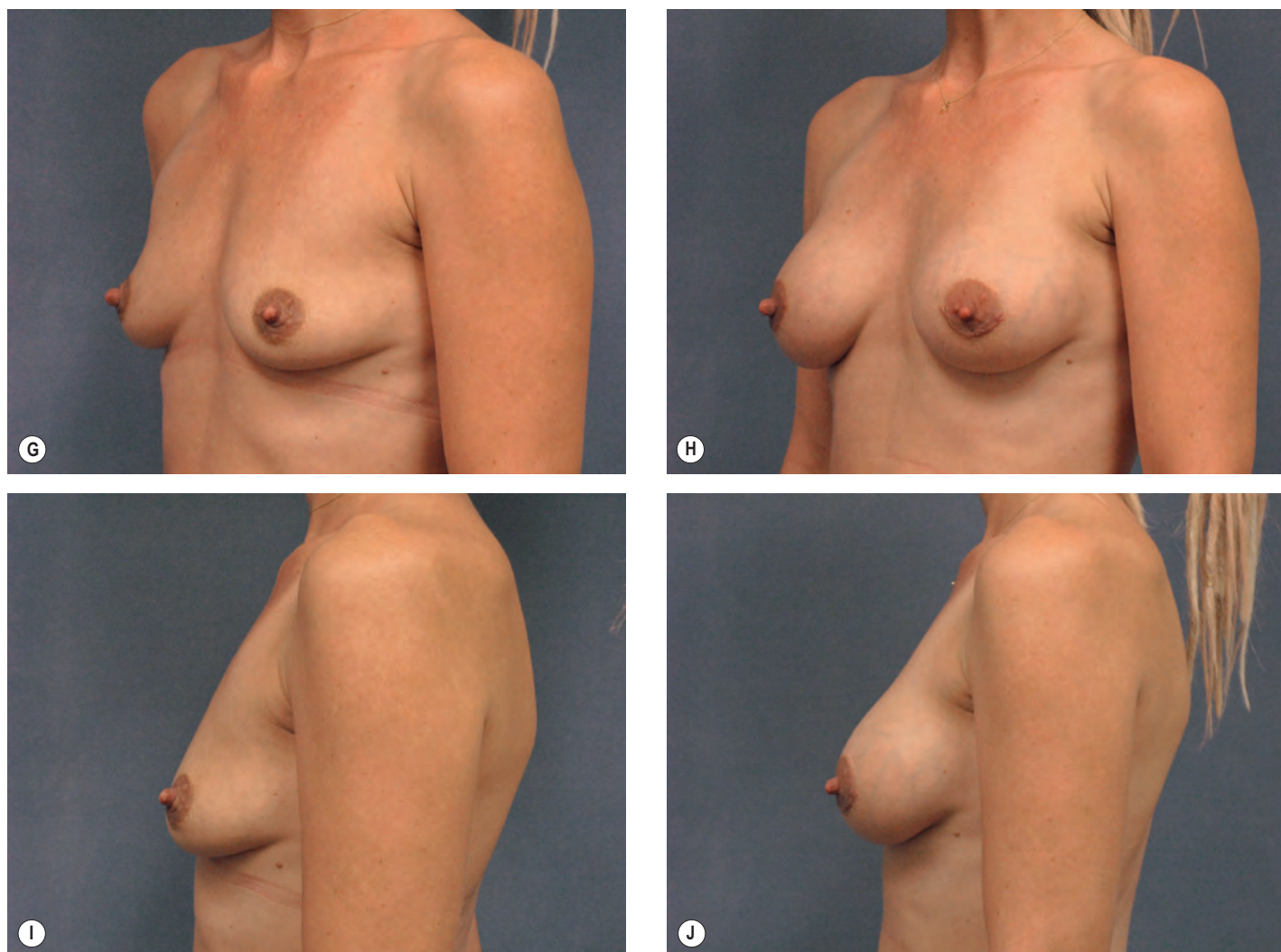


Fig. 7.6, cont'd Left oblique: (G) Pre- and (H) post-procedure. Left lateral: (I) Pre- and (J) post-procedure.

blue paper photographic panties (“modesty garments”) to standardize the clothing, color and white balance. Almost invariably otherwise, a patient would arrive on a subsequent visit with different color, contour and texture of undergarments. In addition, sometimes patients will arrive with a distracting, different dark-light tan line in summer climes. Legs should be slightly apart to allow viewing of the groin against the light background. Feet should be aligned with appropriate tape marks on the floor.

Lower extremity

The five standard views should also be supplemented by a posterior view (Fig. 7.9). The patient should stand comfortably erect with arms folded above the chest. Feet should be approximately shoulder width apart, aligned with appropriate tape marks on the floor. For a full view, the upper margin should be found at the level of the umbilicus and the lower margin inferior to the toes or heel depending on the view. For the half upper or lower view, the lower or upper margin, respectively, should be just below the knee at the level of the

inferior popliteal fossa or just above the patella. The photographic background must extend onto the floor, all the way out of the frame for the lower view.

Hands and feet

A full dorsal and volar view is required. In some patients, oblique views are required as well. Dynamic views in flexion and extension are an essential component of the complete medical record (Fig. 7.10).

Specialty views

Other regions of anatomy follow the same principles: (1) clear margins of background or adjacent anatomy; (2) AP, lateral and oblique views; (3) dynamic views as indicated; and (4) macro views when required to demonstrate features of anatomy.

In the hospital and operating room

The compact digital camera has largely supplanted the 35 mm film camera in the emergency department and on the go.

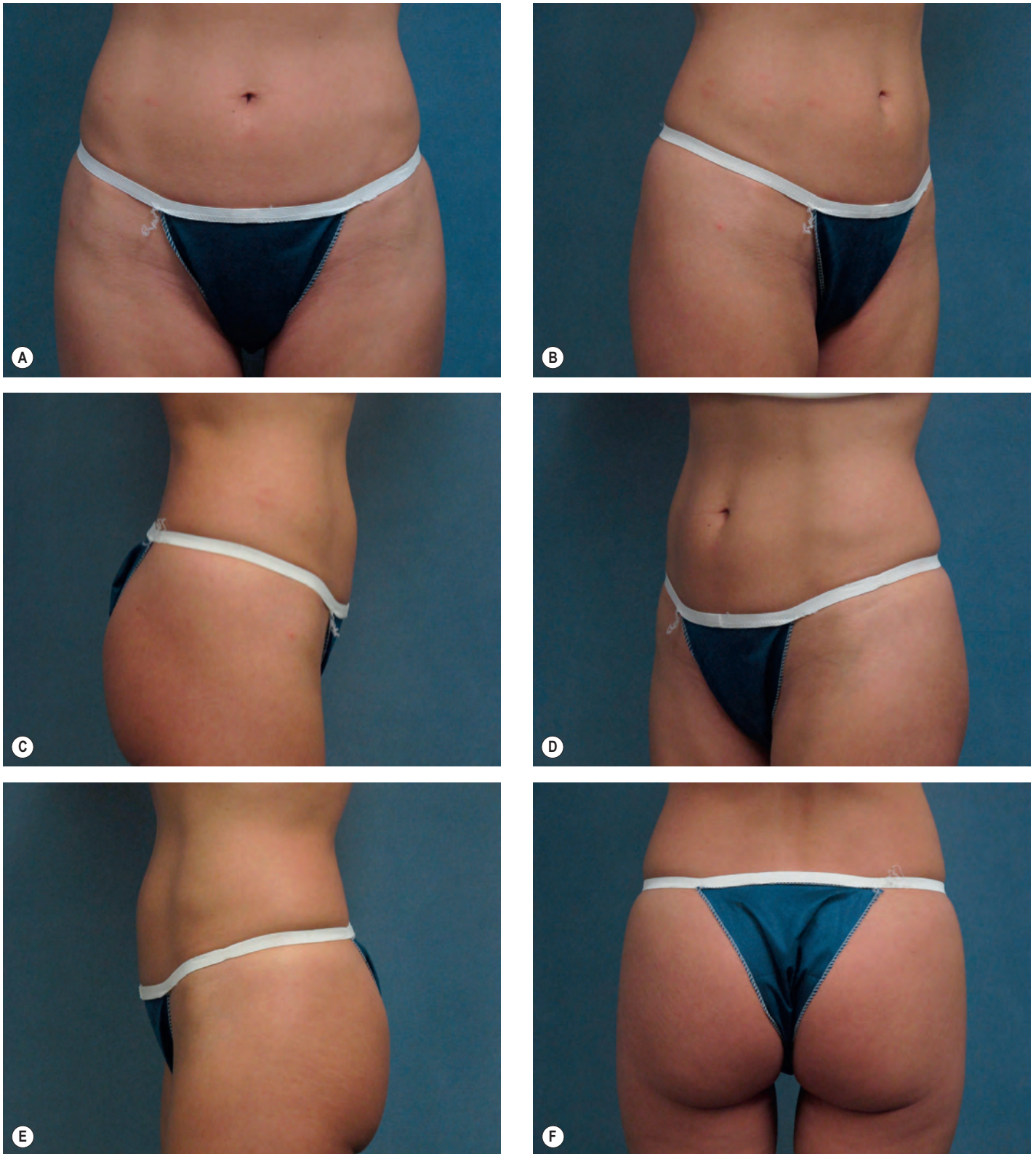


Fig. 7.7 Lower trunk, abdomen and buttocks. Standard views: **(A)** Anterior–posterior. **(B)** Right oblique. **(C)** Right lateral. **(D)** Left oblique. **(E)** Left lateral. **(F)** Posterior view.

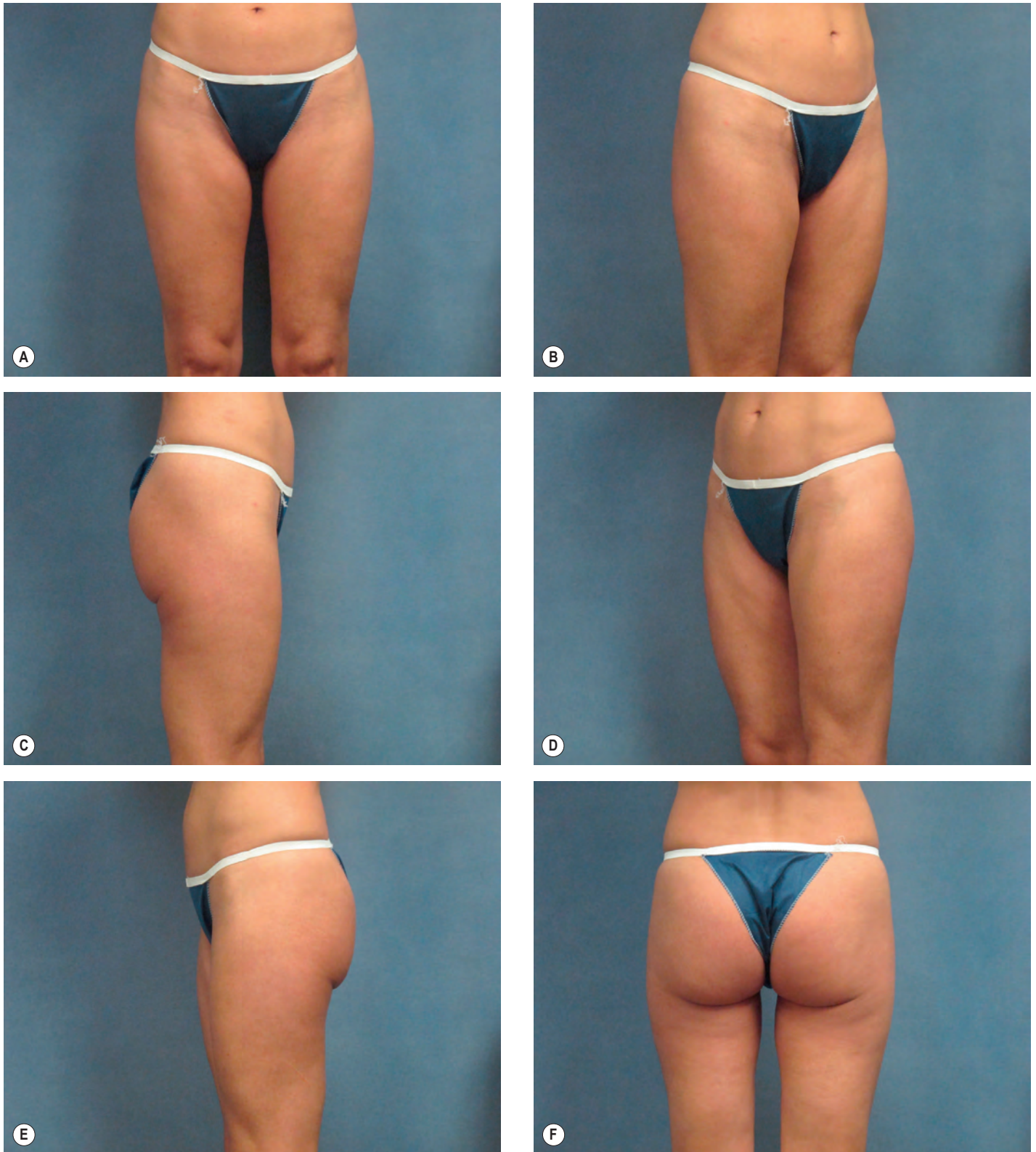


Fig. 7.8 Lower abdomen, buttocks, and thighs. Standard views: (A) Anterior–posterior. (B) Right oblique. (C) Right lateral. (D) Left oblique. (E) Left lateral. (F) Posterior view.

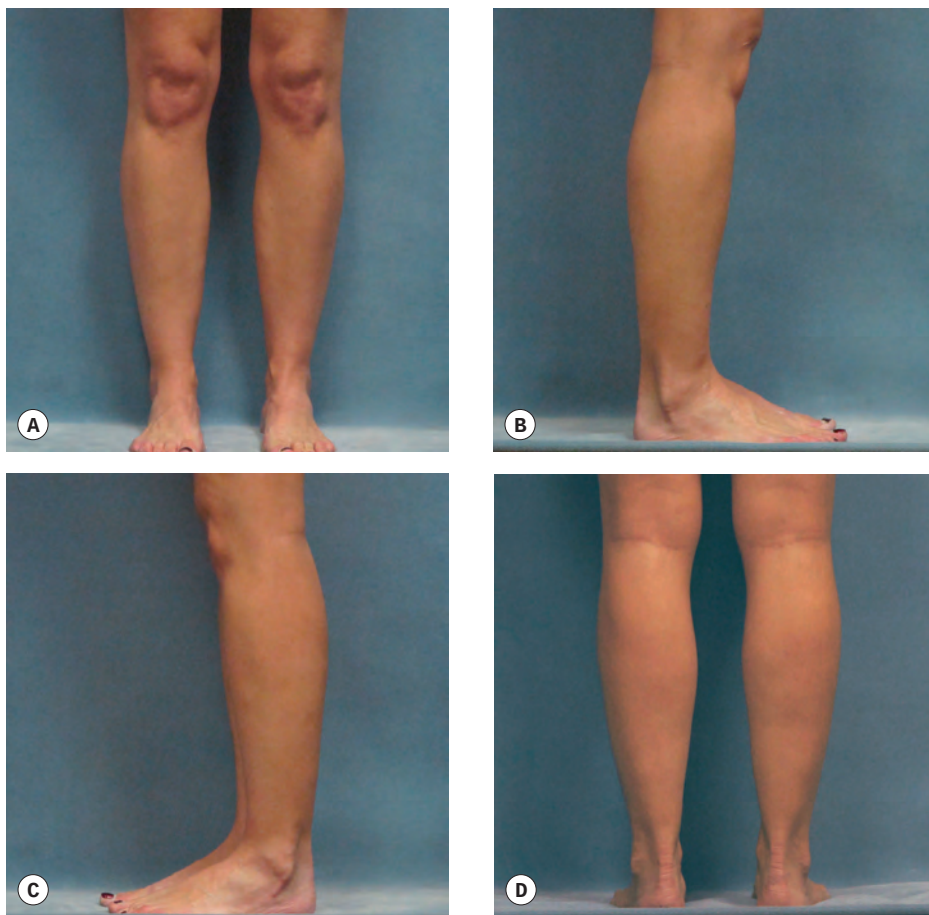


Fig. 7.9 Lower extremity. Standard views: (A) Anterior-posterior. (B) Right lateral. (C) Left lateral. (D) Posterior view.

Results are excellent, and convenience is high. However, when expense is not an issue, many surgeons prefer SLR-like full-frame (35 mm diagonal) digital cameras in the operating room. Operating room lights vary among hospitals and rooms. On-camera hot shoe flashes for large format cameras are of much higher quality than built-ins for compact cameras. This allows for consistency in color balance, as ambient light does not provide the illumination for the exposure. Flashes that are designed for medical photography include the ring flash, dual-point flash, and the ring and point combination flash. The ring flash is particularly useful for intraoral anatomy and intraoperative photography, though it may wash out color and skin tones. Standardized use of auto white balance without a flash in a compact camera is a close second. Macro-mode or close-up focusing may put sterility of the operative field at risk and is more problematic. Automatic exposure reliably creates an image with proper lighting in the operating room.

The need for proper composition of the picture remains in the operative setting or emergency department and may be overlooked amidst other priorities. The framing principles already discussed should be followed to the extent allowed by the sterile field and drapes. Anatomic landmarks should be included at the borders of the frame. Shiny instruments, stained surgical drapes, gauze or glare from overhead lights must be eliminated or covered. Often the overhead lighting is harsh and must be removed from the field to prevent oversaturation of the image.

Archiving and image management

Cameras

There are many excellent resources in the literature for discussions on film photography. The era of light sensitive silver halides suspended in a gelatinous emulsion in film photography resides in niche markets, essentially outside the field of plastic surgery.¹⁶ Film or analog photography had an amazing 160-year run from the 1840s, before being supplanted by digital, around the new millennium.¹⁷ Because the overwhelming majority of cameras in use today are digital, we will concentrate here on digital. Like a film, digital imagers generally consist of red, green, and blue filters. Film has continuous stacked emulsions or layered films of colors, while digital uses variations on a checkerboard pattern of cells to filter light. In the Bayer pattern, most commonly found in digital cameras, every other pixel is green, while one in four is either red or blue. A few cameras, like those from Canon, use a complementary metal oxide semiconductor (CMOS) sensor, but most use charged couple devices (CCDs). In the former, each element contains its own transistor and circuitry providing for independent reading of data. When photons strike a CCD, charges propagate down each row of the checkerboard pattern and this limits the speed with which they can propagate. Newer CCDs have triple-stacked sensors (red, green, and blue, RGB) that lower resolution, but increase sensitivity.

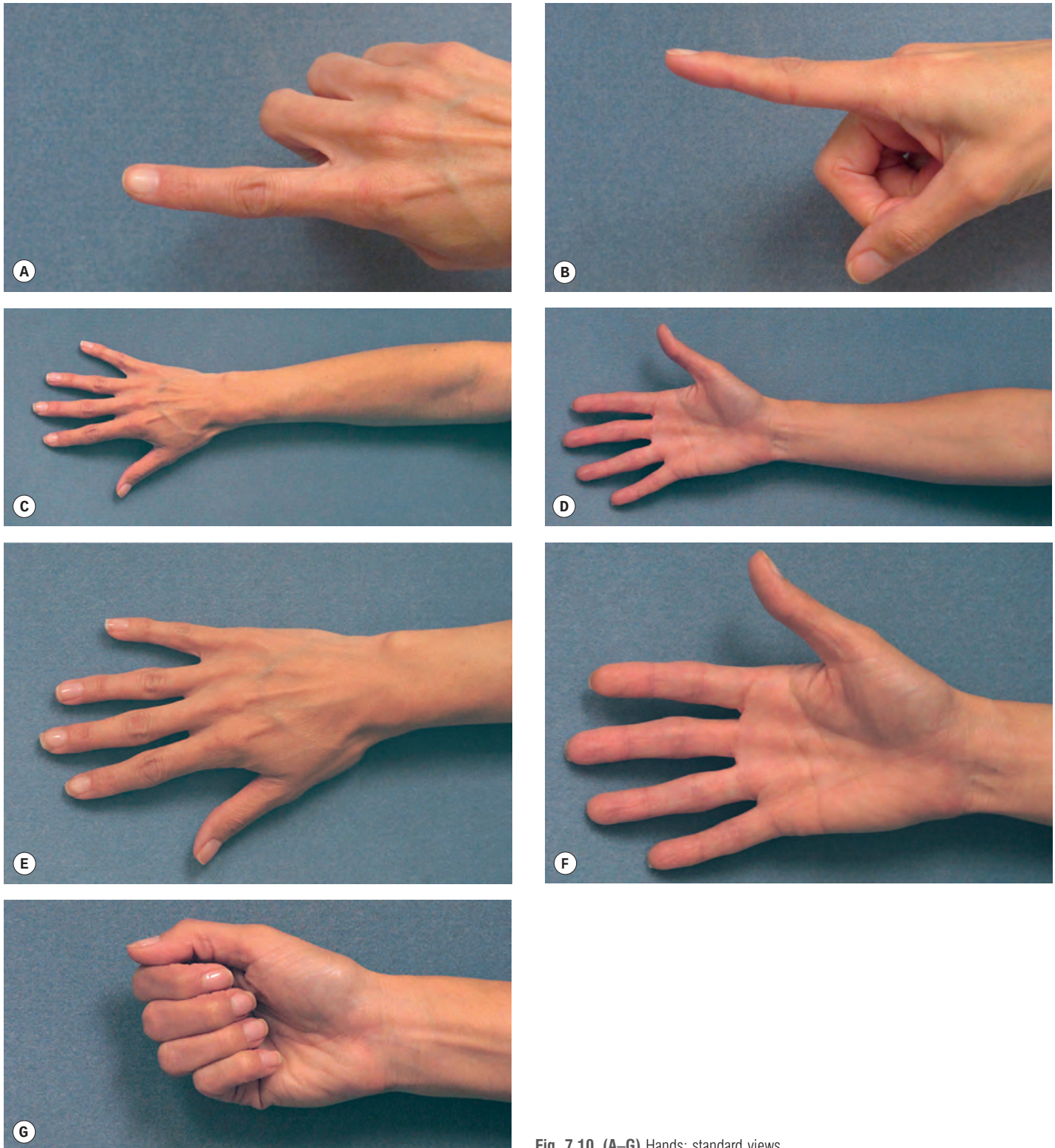


Fig. 7.10 (A–G) Hands: standard views.

Well-designed cameras of either type will capture excellent images.

Choosing a digital camera can be overwhelming due to the myriad of choices available. Even a simple point and shoot can take excellent photos due to unrelenting commercial competition among manufacturers and the decreasing cost of

components. However, the plastic surgeon will require something more capable, albeit a large format, 35 mm size digital camera is not truly essential for adequate pre- and postoperative photographs in the proper setting. Mobile phone cameras are inadequate, as are entry-level compact devices. Lifestyle and fashion cameras are not suitable.

There were “resolution wars” in marketing cameras 10 years ago, but gladly those are over. Resolution is most often used to describe how many pixels are in the array. Minimum sizes now are $>3000 \times 2000$ or 6 megapixels. Actually, most cameras are capable of ≥ 16 . The number of pixels sets the upper limit of image quality, but not the lower limit. Another more important gauge of resolution is how sharply an image resolves fine detail, often depicted by extremely small, narrow lines. This is a more functional definition, though less commonly used.

The enthusiast compact category is generally adequate for plastic surgeons to use on a daily basis, if the additional expense of a prosumer or professional digital camera is not within the budget. Numerous features are available: high pixel count, large sensor size, an advanced hardware algorithm for interpreting the light image that strikes the chips, zoom and video capability are highly valued. Perhaps most important is the quality of the glass and the design of the optics in the lens itself. Features such as rapid shutter speed, geotagging, or very large aperture are not so critical in the patient-care setting. However, enthusiast cameras are capable of capturing images almost indistinguishable from higher end models in a controlled setting such as the plastic surgeon’s photography studio or the operating theater. Prosumer cameras have many of the features of a digital single lens reflex (DSLR). In essence, a plastic surgeon only requires a 50 mm equivalent and a 100 mm equivalent lens setting. Advanced computer design of camera zoom lenses has allowed for excellent shooting characteristics with compact cameras in both the 50 and 100 mm range, with minimal degradation of image quality. In other words, it is possible to get along with an enthusiast or prosumer camera in most situations.

Professional DSLRs are larger, heavier, machined to precise specifications, resistant to moisture and impact and sturdy, with full-frame 36×24 mm sensors that can potentially capture up to 25 megapixels in one image. Medium format cameras with pixel counts up to 60 million are rarely found or required in our specialty. The mirrorless interchangeable-lens camera is a newer class of digital system cameras that is gaining popularity. While they do not have a mirror reflex optical viewfinder, these cameras have been manufactured with various sensor sizes up to full-frame. Compared to DSLRs, mirrorless cameras are smaller and sturdier, while maintaining the versatility of interchangeable lenses. Almost all enthusiast cameras allow for high-definition video recording of several minutes duration. This is entirely adequate for documenting repeated key steps in an operative procedure, while not reaching the standards of a professional cinematographer.

Format

Storage

Digital memory cards come in a variety of types including compact flash and secure digital (SD). They are capable of transferring data at up to 30MB/s for high resolution video such as full HD or 4K video. HD resolution may be 720p based on vertical dimension (1280 pixels wide by 720 pixels high) or 1080i/1080p (1920 by 1080 pixels), with horizontal lines scanned interlaced (i) or progressively (p). 4K resolution

refers to a display device or content having horizontal resolution on the order of 4000 pixels. Under the previous convention, 4K would be equivalent to 2160p.

Secure digital media come in a regular or high capacity format (SD, SDHC, or SDXC). Recently, 128 GB and even 512 GB models are available worldwide with speed adequate to capture video at high resolution. Micro-SD cards are generally relegated to mobile phone cameras and data storage.

Memory card readers are widely available and inexpensive, like memory cards. Data can be uploaded to a computer via USB cable attached to the camera from the computer. However, it is quite common to remove the card, insert a spare into the camera and read the data from a card reader.

With the advent of the multi-terabyte hard drive, both desktop and portable, storage of thousands or tens of thousands of pictures is no longer an issue. Maintaining a disciplined, regular back-up program, however, is as essential as any record-keeping in the practice. At least two copies should be maintained onsite, and another offsite at a remote location to obviate water, fire, or earthquake damage.

File formats

There are dozens of data structures or architecture, also known as file formats. We will only concentrate on a few of the most commonly used: TIFF, JPG (or JPEG, for joint photographic experts group), Photoshop, GIF and RAW. Fortunately, almost any software will convert one still image type to another. However, it is important to understand their advantages and disadvantages.

TIFF is best used for print reproduction because it is a bit-mapped (like a printer) or raster Tag Image File Format. It supports 24-bit color depth per pixel, dimensions and color look-up tables “tagged” to the header of the data file. The way the tag specification is written gives rise to various versions of a TIFF file. Lossless compression with the LZW algorithm makes compression safe for data quality.

JPEG (JPG) is perhaps the most common file type, and it is “lossy”. Compression can be chosen from a 12-part scale from none to as much as 90%, while data quality diminishes accordingly. For quick exchange of images via email, this is ideal. Minimal compression almost retains original image fidelity. There is almost no software that cannot easily read this format, and with wide latitude in software storage parameters there is great flexibility.

Photoshop (PSD) is a proprietary format of Adobe Systems Corporation (San Jose, CA), but is so commonly used as to almost be a standard. Color management, 48-bit color and layers are supported.

RAW format varies from camera to camera because it is dependent on the hardware interface with the light capturing chip (CCD or CMOS) inside the camera. These files are sometimes called digital negatives because they fulfill the same role as negatives in film photography. It is the truest image as there is no white balance, color processing, compression, sharpening, or other manipulation of the data. Because the data is unprocessed, capture rates can be much faster with higher throughput. RAW has numerous advantages over JPEG including higher image quality, finer control, non-destructive change capability, and lossless compression. However, camera RAW file size is typically 2–6 times larger than JPEG files, and

lack of standard RAW image format requires more specialized software to open RAW files.

Video, unfortunately, is plagued by numerous incompatible standards. Even file formats with identical suffixes may be unreadable by other software or hardware, e.g., MP3 or MP4 (motion picture experts group 3 or 4) are often not readable unless the original software used to create the file is available. A software codec (coder-decoder) is required and often not cross-platform for PC or Mac. That rigorous discussion awaits another setting.

Image attributes, metadata, and retrieval

As the images are safely transferred to storage media, critical new information must be attached to the data. Modern cameras use a format called EXIF for recording camera type, lens, date, time, shutter, aperture, and many other items. Even more critical for plastic surgery is information like patient age, sex and weight, ICD-10 diagnostic codes, CPT procedural codes, type of implant used, pre- or postoperative status, date of original surgery and other critical pieces of medical data. These are proprietary to individual software packages and make changing platforms difficult after even a few months or a year of use. What once was a demanding and difficult exercise is now made transparent and easy by improved software interface designs.

The Health Insurance Portability and Accountability Act of 1996 (PL 104-91) has resulted in a major increased emphasis on patient privacy among other concerns. The broad interpretation of this law includes any part of the medical record. The American Recovery and Reinvestment Act of 2009 extended Privacy and Security Provision of HIPAA to business associates of covered entities and provides for stiff civil and criminal penalties for violation. Loss or dissemination of digital images can be much more serious than film photographs, with the risk of electronic data “going viral” over the internet to millions of people.

Digital image processing

Measurement and analysis

Orthognathic surgery has rested on the principles of image measurement and analysis since the early days of film photography. Measurements were made directly on photographs or transparencies and taken to the operating room to guide surgical osteotomies. Now these measurements can be made directly on the digital image. A well-developed model of cleft lip repair has been incorporated into the training program for a large charitable organization prior to surgeons going overseas on mission work.

Identifying and highlighting anatomic landmarks for the medical record in breast augmentation surgery increasingly has become a part of the preoperative consultation.¹⁸ It is the first step in building a predictive model for planning pocket dissection, choosing implant size, evaluating postoperative size and may lead over time to reduced rates of re-operation.

Planning and simulation

The term surgical simulation has been broadly defined to include anything from computer-assisted tutorials to

interactive learning to engaging in mock surgery with haptic feedback and complete with unexpected complications.¹⁹ Surgical planning is more easily achievable, and requires less computer power and complexity in programming. Organized medicine was challenged by the Institute of Medicine Report, *To Err Is Human: Building a Safer Health System* in 2000.²⁰ It has been estimated that 44,000 deaths occur yearly due to medical errors, the seventh leading cause of death. Many of these occurred during surgery, as a result of surgical planning or postoperative care.

Computer-based virtual surgical planning (VSP) is generally available in plastic surgery from commercial companies (Nex-Tech, Stryker, Canfield, and CrisaliX). Standardization of patient topographical measurements can be utilized to enhance preoperative planning and improve postoperative outcomes. More elaborate mannequin-based systems are becoming more mainstream due to the advent of 3D printing. Customized implants and prostheses have been used throughout plastic surgery, and the integration of precise anatomical topography in the preoperative setting with 3D printing could revolutionize the world of implants in plastic surgery.

New frontiers

Three-dimensional surface imaging

In conventional medical procedures, diagnosis, treatment, and outcome are typically judged by objective criteria. The patient's subjective feelings are of relevance, but of a secondary nature. In plastic surgery, on the other hand, the healthcare model is often one of wellness and enhancement, the patient is not ill or diseased and therefore the diagnosis, treatment, and outcome may be dominated by the patient's subjective assessment of an elective surgical procedure. Consequently, even the most technically perfect surgical procedure can lead to patient dissatisfaction, should the result not meet aesthetic and psychological expectations. Failure to meet these expectations can lead to the need for re-operation, increased medico-legal risk and additional costs directly to the surgeon. Furthermore, the market dynamics of cosmetic surgery are strongly driven by patient referrals, which again are based upon patient satisfaction. In breast augmentation surgery, for example, it can be advantageous that the patient is collaboratively involved in the process of implant selection, supported by the surgical team, and that the patient ‘buys in’ to the selection process with enthusiasm, confidence and conviction. One of the major reasons to undergo plastic surgery is to change the external appearance of the patient; a central question that all patients have in common is “how should I look after my operation?” One way to answer this is through 3D imaging.²¹

Today, 3D physics-based finite element analysis (FEA) technology can provide patients with a simulated view of their anatomy in a postoperative condition. While there are other methods to show the patient a probable outcome – such as special bras and sizers, computer slide shows with various before/after photographs of previous patients, collecting photographs from magazines, and morphing software based on photographs – all have limitations. All these methods require realistic imagination by the patient. State of the art technology allows patients to see themselves from varying

angles in 3D before the operation, increasing communication with the surgeon by interacting collaboratively with the image, and simulating the outcome of the surgical procedure.

Techniques for 3D modeling include, on one hand, expensive, space-limited and obsolescence-sensitive hardware scanners, and on the other hand, those based on the physical reconstruction of the body from 2D photographs. The former requires a large upfront investment amortized over time. The latter method functions on a pay-as-you-go basis and takes advantage of ease of use, simplicity, and minimal interference with the way the surgeon performs a consultation. When no special hardware is required, photographs are coupled with anatomical measures and physiologically-based data processing and simulation. Whatever technique employed, 3D and virtual reality are the future.^{22–26}

Video

Much of what has been said of 3D technology can be said of video medical records, other than the simulation aspects. Motion picture film has been a part of medicine for decades for surgical education, while digital video as a part of a medical record is a recent and evolving innovation, not yet standard of care. Almost every modern digital camera has the capability of capturing video clips. However, the lenses are not specifically designed for professional quality where heavy, expensive equipment is required and more computer power and capability is mandatory. Creation and routine use of detailed video is beyond the scope of most busy plastic surgery practices, though it provides a method to augment surgical education and analyze personal operative

performance. It obligates a commitment to production values, editing, composition, and a host of skills residing in the professional medical videographer. Short videos can document features such as range of motion, bulk strength and tone, elasticity and even aesthetic contours in motion. However, long compositions require expert direction, videography and editing. One potentially cost-effective solution is the use of commercially available amateur point-of-view video systems in the operating room. The future will certainly increasingly incorporate digital video in the practice of plastic surgery.²⁷

Presentations

In the era of digital media, the art of medical presentation should be mastered by every plastic surgeon to educate patients, students of surgery, and other healthcare providers. The nature of our specialty encourages photography and videography to take center stage in a digital slideshow.

Key principles

- When creating slides, think big font and limited text.
- Cite examples and use case presentations.
- Utilize appropriate animations to illustrate techniques and concepts.
- Use emphatic and descriptive gestures during live presentation.
- Ask effective questions to engage the audience.



Access the complete reference list online at

<http://www.expertconsult.com>

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Patient safety in plastic surgery

Bruce Halperin[†]

SYNOPSIS

- Modern medicine has greatly reduced the risk of surgery.
- Identifying which patients are at greatest risk for surgery starts the risk reduction process.
- Identification of medical factors leading to complications helps prevent untoward outcomes.
- Specialized care for the liposuction patient.
- Specialized care for the patient having facial aesthetic surgery.
- Avoiding fire in the operating room.
- Protocol-based systems for risk reduction.
- Reducing patient risk through optimal patient care.
- Do it better, do it safer.

The risk of having surgery

The decision to perform surgery to correct a defect or medical condition begins a cascade of decision-making and, by necessity, a series of compromises. It is the underlying desire of the medical profession to prolong and enhance the lives of patients who seek attention. Since the beginning of the practice of medicine it has been understood that undesired outcomes may occur. The acceptance by the patient of undesired outcome has changed over the course of medical history. As medical science has progressed, the expectations of patients and the medical profession have risen. As medical science understands ever-increasing levels of human biologic complexity, the expected outcome from medical intervention may change yet again. It is not yet clear to the practicing physician or public as to the fundamental cause of undesired medical outcomes.

It is clear that many of the undesired outcomes we now see are a result of failure to implement knowledge we already possess. We must further question whether it is our healthcare

delivery system that is in fact responsible for many of the undesired outcomes that our patients face. When we decide to perform a surgical procedure we accept the risk of undesired outcome. Using the knowledge gained from scientific studies, we select what we believe to be the “best” path to resolution of the patient’s condition. The question in our minds must always be: What is the “best” pathway in this particular surgical case?

Prior to the introduction of anesthesia the surgical experience was a decidedly unpleasant one for the patient. The success of a surgical procedure (read: survival) was often based on the speed at which the procedure was accomplished. If nothing else, the introduction of anesthetic techniques brought the ability of the surgical team to take more time in accomplishing the procedure. The introduction of an additional medical intervention (anesthesia) on the patient brought additional undesired effects and perioperative death.^{1,2} Since the introduction of general and regional anesthesia as part of normal surgical practice, surgical and anesthetic complication rates have been analyzed using a variety of clinical criteria. It is this wide variety of criteria that has led to confusion in the medical literature and in the mind of practicing clinicians of the actual risk attributable to anesthesia care during a surgical intervention. Do we consider in our complication rate only events that happened during the actual surgical procedure? Do we only consider events attributed solely to providing anesthesia or do we consider the contribution of surgery to the untoward outcome?³ The time course for evaluation of surgical and anesthetic complications remains controversial and almost certainly is related to the nature of the surgical procedure and type of anesthesia, if any, that was used during surgery. The wide variety of time indices that are used in the medical literature for the study of perioperative complications makes comparison of studies very difficult. Definitions of the time period for study of perioperative mortality range from 48 hours, as defined by the Joint Commission on Accreditation of Healthcare Organizations, to 30 days, as defined by the American College of Surgeons. Similarly, the inability to compare clinical studies adds to the confusion in defining

[†]Deceased

Table 8.1 ASA classification

ASA I	Normal healthy patient without active disease
ASA II	Patient with mild systemic disease (e.g., hypertension under medical control)
ASA III	Patient with severe systemic disease
ASA IV	Patient with severe systemic disease that is a constant threat to life
ASA V	Patient who is moribund and is not expected to survive without surgery
ASA VI	Patient who has been declared brain-dead for organ donation
ASA, American Society of Anesthesiologists.	

clinical risk to the patient from a given surgical or anesthetic technique. For anesthetic risk we need to consider not only cases where anesthesia is deemed the sole cause of complication and mortality but also cases where anesthesia is a significant contributing factor of complications and mortality.

It remains extremely difficult, even with review of the extensive body of medical literature, to predict accurately the risk for any given patient who is about to undergo any given surgical procedure. We can confidently claim that complications from anesthesia have been greatly reduced since the widespread acceptance of modern anesthetic techniques. Beecher and Todd published in 1954 that, where anesthesia was a very important contributing factor, death occurred in 1:1560 surgeries.⁴ Today, patients want to know the current state of the art of medical science in regard to perioperative risk and complication. One of the most useful and popular ways to assess risk in the surgical patient population is by the American Society of Anesthesiologists (ASA) physical status. This classification system was originally designed in the early 1940s and updated in 1961 (Table 8.1).

The ASA classification system has been shown to correlate with surgical and anesthetic outcome.⁵ Lagasse's study⁵ concluded that the incidence of anesthesia-related mortality within 48 hours of surgery was 1:13000 procedures, when evaluating all patients coming for a surgical procedure. Of great interest, but of little surprise to the practicing anesthesiologist, was that anesthesia-related deaths increased with increasing ASA classification. Other reports dating as far back as 1987 report anesthesia-related mortality rates at 1:185000.⁶ The study by Buck *et al.*⁶ was performed before the widespread acceptance of new technology monitoring systems (pulse oximetry and capnography) that serve as early-warning systems for respiratory compromise. More recent studies have shown even better safety outcome results for patients having surgery. A 2004 study performed in France again showed that mortality rates increased with increasing patient ASA status,

at a rate of 4 deaths per million surgeries for ASA category I patients and with 554 deaths per million in ASA category IV patients.⁷ The effect of medical progress on improved clinical outcome is often difficult to detect when the incidence of maloccurrence is infrequent. Significant changes in daily anesthesia practice began in the mid-1980s with the introduction of the Harvard Standards of Practice I – minimal monitoring. These anesthesia standards required the use of monitoring devices to detect and prevent impending disaster during surgery.⁸ The 1986 ASA standards for basic intraoperative monitoring encourage both capnography and pulse oximetry during conduct of anesthesia and surgery. The incidence of accident and death rate in ASA status I and II patients was studied before and after the adoption of the new monitoring standards at Harvard hospitals (Table 8.2). The implementation of these standards, along with the introduction of new monitoring techniques, has greatly reduced the incidence of unrecognized hypoventilation and hypoxemia leading to intraoperative complication and death.⁹⁻¹¹

The implications of these findings for current clinical practice in the operating room are clear. Monitoring equipment for electrocardiogram, blood pressure, pulse oximetry, capnography, inspired concentration of oxygen on anesthesia machines, and temperature must be available in the operating room, functioning and used in all appropriate situations. The proper use of monitoring devices during surgery improves safety during surgery. Nonfunctioning monitoring equipment postpones surgery.

It is the experience gained from in-hospital surgery and advances in medical care that have allowed the development of outpatient surgery. Recent data show that upwards of 60% of surgery at community hospitals in 2005 was performed in an outpatient setting.¹² It is almost certain the percentage of patients undergoing cosmetic and reconstructive surgery on an outpatient basis is even higher. In the mid-1970s there were two free-standing outpatient surgery centers in the US. There are now over 5000. The success of outpatient surgery done outside a hospital operating room is based on the cost-efficient ability of these centers to meet the medical needs of the patient and the medical staff safely. It has been shown repeatedly that outpatient surgery can be performed with a safety standard equal to or exceeding that available in an inpatient hospital-based environment. The spectrum of settings for performance of surgery continues to expand with the development of office-based surgical facilities.¹³ The American Society of Plastic Surgery through the Patient Safety committee has published an outstanding series of articles outlining advisory principles for safety in ambulatory surgery.¹⁴ These reports, based on the medical literature combined with the general principles described above, set an educated guideline for conduct of outpatient plastic surgery. A primary area of concern for the plastic surgeon is patient selection for surgery

Table 8.2 Incidence of intraoperative anesthesia complications

Dates	ASA status I and II patients (n)	Intraoperative accidents (n)/incidence		Death (n)/incidence	
1/1976–6/1985	757000	10	1/75700	5	1/151400
7/1985–6/1988	244000	1	1/244000	0	0/244000
Monitoring standards instituted 7/1985. ASA, American Society of Anesthesiologists.					

and whether or not to perform the surgery on an outpatient basis. We have previously described the data that demonstrate that complications increase with an increase in a patient's ASA status. Prospective stratification of 17 638 patients by age found that patients over the age of 65 years were 1.4 times as likely to have an untoward intraoperative event and twice as likely to experience an intraoperative cardiovascular event as patients under 65.¹⁵

Obese patients/sleep apnea patients having plastic surgery

Multiple studies have demonstrated an increase in perioperative risk associated with obesity. Complications during surgery associated with patient obesity include increased rates of failed regional anesthesia, unplanned hospital admissions, and an increased incidence of deep venous thrombosis.¹⁶ It is also unreasonable to expect medical care providers to be able to manage the obese patient physically without assistance from other healthcare assistants. Unless an ambulatory center is prepared to have the help the obese patient will require, the patient should have surgery in a facility with the necessary staff available. Setting a weight limit for patients, based on the ability of the staff of the center to manage the patient, avoids uncomfortable situations when the patient arrives for surgery and the facility is unable to take care of him or her. Proper planning at the surgical facility reduces surgical cancellations. Obese patients have a higher incidence of sleep apnea than patients of normal body habitus. Physical characteristics that predispose patients to having obstructive sleep apnea include body mass index over 35, neck circumference of 17 inches (43 cm) in men or 16 inches (41 cm) in women, craniofacial abnormalities affecting the airway, nasal obstruction, and tonsil hypertrophy.¹⁷

The 2006 report by the ASA taskforce on perioperative management of patients with obstructive sleep apnea is a valuable reference for conduct of care of this classification of patients.¹⁷ The severity of sleep apnea, as determined by a formal sleep study, is seen in Table 8.3. The severity of oxygen saturation depression during apnea events and the number of apneic events per hour should be considered in evaluating the patient for surgery.

Proper perioperative clinical management of patients with sleep apnea is of critical importance. Airway management of the obese patient, with or without sleep apnea, may be difficult. Careful airway evaluation preoperatively with notation of mouth opening, mental-hyoid distance, submandibular compliance, range of motion of the cervical spine, and

Mallampati score may indicate potential difficulties in airway maintenance and intubation.¹⁸ Conduct of the actual anesthetic for patients with a history of sleep apnea and having plastic surgery depends on many factors. Certainly the type of surgery, the severity of airway disease, and the desires of the patient are major components in the decision-making process. The need for intubation or airway manipulation during surgery should not be an automatic exclusionary criterion for outpatient surgery in a patient with a history of sleep apnea. Appropriately selected patients with a history of sleep apnea who are observed and monitored for extended periods of time after surgery may do well on an outpatient basis. Patients with sleep apnea requiring large amounts of postoperative narcotics or sedatives and those who are noted to have decreased oxygen saturation levels on room air or inadequate ventilation will require admission and continued monitoring in an acute care setting. Monitoring of the sleep apnea patient after surgery and after hospital admission includes continuous oxygen saturation. Monitoring of oxygen saturation levels on an every 4–6-hour basis makes no sense given the fact that obstructive apneic events are more likely after surgery and hypoxic brain injury may occur in a matter of minutes.

In addition, it may be unwise to attempt to complete a surgical procedure on a patient with sleep apnea using local anesthesia with deep levels of sedation. Commonly used medications for sedation during surgery, including narcotics and benzodiazepines, may exacerbate apneic episodes leading to hypoxia and hypoventilation. Performing procedures on a patient with sleep apnea with the patient in the prone position and limited airway access without first securing the airway may be particularly hazardous. It is often difficult to monitor ventilation accurately in a nonintubated patient. New technologies to detect hypoventilation will need to be developed to monitor ventilation accurately in nonairway-controlled patients. Development of continuous arterial CO₂ monitoring using a noninvasive format will further improve patient safety during surgery.¹⁹ Patients using continuous positive airway pressure (CPAP) as a therapeutic modality for sleep apnea should be instructed to bring the CPAP equipment to the surgical center. The center should have personnel knowledgeable in the application of CPAP devices available to assist in the respiratory care of the patient. Similarly, patients who use CPAP at home should use their CPAP while resting or asleep at the hospital.

Despite careful attention to airway evaluation, clinical experience and prospective studies have demonstrated a relatively poor ability of the medical practitioner to predict which patients will have a difficult airway. Upwards of 3% of patients deemed to have “normal” airways may have difficulty with intubation. The implications of our inability to predict which patients will have a difficult airway include the need to have an extensive selection of airway management tools available in the surgical setting where airway complications may arise. In addition to the traditional array of laryngoscopes and blades, airways, and endotracheal tubes of many sizes comes the need for fiberoptic laryngoscopes, laryngeal mask airways, and the personnel who can readily use these tools. Newer technologies, including video laryngoscopes, should be available to those trained in these techniques. It is not a question of how much equipment you can purchase, but which equipment you are skilled at using during an emergency to establish an airway. Every surgical facility should

Table 8.3 Criteria for determining the severity of sleep apnea after sleep study

Severity of obstructive sleep apnea	Adult apnea–hypopnea index	Pediatric apnea–hypopnea index
None	0–5	0
Mild	6–20	1–5
Moderate	21–40	6–10
Severe	>40	>10

be capable of performing a surgical airway (tracheostomy) in the rare case of failed airway management.

Review of large databases evaluating the safety of surgery has shown that surgery and anesthesia are very safe. The risk of anesthesia as the cause of death in ASA I and ASA II category patients is in the range of 1:150 000–1:300 000 patients.^{20,21} Therefore, it should be no surprise when medical publications are presented with a small series of patients undergoing outpatient surgery in an office-based surgery center that the reported complication and death rates are very low.²² In a study on office-based surgery, 84.3% of patients were ASA class I, 15.6% ASA II, and only 0.1% ASA class III. It would require a very large data collection of ASA I and II patients to provide evidence of increased risk or an improved outcome in a particular surgical setting or using a specific anesthesia technique in this subset of patients.

Similar publications have documented the highest levels of safety in the office surgery environment using general anesthesia. Hoeflin *et al.* published a series of 23 000 consecutive surgical patients over an 18-year period. The advantages of general anesthesia with airway control during surgery are also presented.²³ Again, given the relatively low incidence of complications in this patient population and the small number of patients studied, it will be difficult to show statistically significant change in clinical complication rates. The American Association for Accreditation of Ambulatory Surgery Facilities study of 400 675 patients concluded that patient safety in accredited office-based surgical facilities was equal to or exceeded the safety level of surgery in a hospital.²⁴ As these articles propose, there are tangible benefits to office-based surgery, including cost containment, convenience, and ease of scheduling. There is little doubt that patients prefer the quieter, gentler ambience of the office/outpatient surgery center as compared to a busy hospital environment. The office-based surgery/outpatient surgical environment can provide a superb surgical environment for patient, physician, and staff as long as the quality of care equals or exceeds that of the full service hospital in all regards.

Intraoperative management of the plastic surgery patient

Both the medical literature and nonpeer-reviewed publications extol the virtues of a variety of anesthesia techniques for plastic surgery, in particular aesthetic surgery. The general public would like to believe that a less invasive and seemingly simpler anesthesia technique will be safer. Physicians who are not knowledgeable of the medical literature may contribute to this misconception. As we have seen in the case of patients with sleep apnea, local anesthesia with deep levels of sedation may not be an appropriate anesthetic choice and may put the patient at substantial risk of airway compromise. Both local anesthesia and general anesthesia produce a similar incidence of complications in patients having oral surgery on an outpatient basis.^{25,26} The 2006 closed claims analysis from the ASA Closed Claims database demonstrated that, relative to the incidence of the anesthesia technique, death during monitored anesthesia care and general anesthesia was twice as common as in patients undergoing a regional anesthetic.²⁷ The primary complication leading to death in this study was inadequate

oxygenation and ventilation. In this closed claim study, respiratory insufficiency was found to have occurred in 15% of patients who had monitored anesthesia care versus 7% of patients who had general anesthesia. Other factors in this group, such as patient age and ASA classification, may have contributed to the findings. Randomized studies comparing anesthesia technique for a given surgical procedure must be performed before declaring a winner in the category of anesthesia technique for patient safety. Very large patient populations will need to be evaluated so that appropriate conclusions can be drawn.

Some anesthesia techniques used during surgery appear to have been poorly evaluated for possible complications. Epidural anesthesia for patients undergoing liposuction appears to expose the patient to large doses of local anesthetics when used in both the delivery of epidural anesthesia and as a component of the tumescent solution. Vasodilation by regional anesthetic blockade of the sympathetic nervous system seems to conflict with the application of dilute solutions of epinephrine for vasoconstriction during liposuction. Again, heavy sedation of a patient in the prone position with a high dermatome level of regional anesthetic seems unwise for patients undergoing liposuction because of concerns with airway compromise and respiratory insufficiency. Despite these considerations, numerous publications have supported regional anesthesia use in this setting. A well-thought-out anesthetic plan that is coordinated with the surgeon and operating room staff will add to patient safety.

Advances in medical technology and medical practice have allowed the development of outpatient surgery to be performed in both a free-standing surgical center and in the medical office-based surgery setting. The American Society of Plastic Surgery commissioned a taskforce on patient safety in office-based surgical facilities and published a taskforce statement.²⁸ This taskforce statement provides conservative judgments on the nature of surgical procedures appropriate for the office-based setting and the appropriate magnitude of these same surgeries. Of particular interest to the practicing physician was the recommendation for limiting the volume of liposuction to a total of 5000 cc of total aspirate volume (fat and fluid). A large study looking at the clinical outcome of 631 large-volume liposuction patients showed a high degree of safety and extremely low complication rates with much larger total aspirate volumes.²⁹ Our current clinical policy limits aspirate volume to 5000 cc of supernatant fat in the outpatient setting and allows aspiration of an additional 1000 cc of fat for patients admitted to the hospital after surgery for continued monitoring. The medical literature provides very little basis for the taskforce recommendations and the medical literature and clinical experience suggest that larger aspirate volumes may be safely performed at a single operation. The physiologic injury of liposuction depends on the surgical technique employed and the body surface area of the patient. Removing 5000 cc of fat from a 100-lb (45-kg) patient will have very different physiologic consequences than the same type of surgery performed on a much larger patient.

Recommendations for limits on liposuction aspiration should be based on appropriate medical and physiologic considerations. Suggestions have been made to limit the duration of a plastic surgery procedure as a method of establishing safe medical practice. Perioperative clinical risk increases

with longer surgical duration. Bringing the patient back to the operating room for a second surgery also involves exposing the patient to additional risk. The decision to perform one longer surgery or two shorter surgeries involves many factors.

The American Society of Plastic Surgery Patient Safety Committee published *Evidence-Based Patient Safety Advisory: Liposuction* in 2009.¹⁴ The use of lidocaine as a component of the wetting solution injected into the fat prior to aspiration has been well discussed in the medical literature. Local anesthetic in the wetting solution is used for two purposes. The first is to reduce the level of additional anesthesia (general or sedation) that is needed to complete the procedure and keep the patient comfortable during surgery. The second purpose is to provide postsurgical analgesia in the body areas where surgery has been performed. Death from local anesthetic overdose has occurred during liposuction. Mistakes have been made in the compounding of the wetting solution used during liposuction surgery. Bottles of 2% lidocaine have been added to the wetting solution when 1% lidocaine was prescribed for compounding. Bupivacaine 0.5% has been added to wetting solutions when lidocaine 0.5% was prescribed for compounding. Catastrophic outcomes have occurred from these errors. The compounding of wetting solutions must be confirmed by two individuals to ensure accuracy and prevent error. Limitation of lidocaine dosing must be conservative because of erratic and unpredictable serum levels of local anesthesia from any given wetting solution administration.^{30,31} Multiple studies have documented that plasma lidocaine levels peak 10–12 hours after wetting solution containing dilute concentrations of epinephrine is injected in the adipose tissue prior to liposuction. For patients undergoing liposuction on an outpatient basis, peak lidocaine levels will occur after discharge from the surgical facility. Following tumescent injection into highly vascular areas of the body such as the neck, peak lidocaine levels occur more rapidly (6 hours) and at higher serum levels.³² In liposuction surgery with large volumes of tumescent injection, sources of additional local anesthetic administration, such as laryngeal tracheal anesthetics, should be avoided by the anesthetic provider. Epinephrine levels peak after tumescent injection at about 3 hours postinjection.³⁰ It has been postulated that elevated epinephrine levels post tumescent injection may contribute to renal blood flow changes, leading to decreased urine output during larger-volume liposuction.²⁹ Perioperative fluid management for the patient undergoing liposuction has been a topic of great debate. Clinical studies and clinical experience have shown that approximately 30% of injected wetting solution is aspirated during liposuction with 70% of the injected tumescent volume remaining in the adipose tissue and subsequently absorbed into the central circulation.^{33,34}

Deep venous thrombosis/pulmonary emboli in the liposuction patient

Risk stratification and institution of appropriate therapy for prevention of venous thrombosis and pulmonary embolism is a key component of perioperative medical management. Preoperative medical evaluation of patients with a history

of coagulopathic disease, venous thrombosis or pulmonary embolism will aid in developing appropriate perioperative strategy for reducing the risk of thrombotic events during and after surgery.³⁵ The use of prophylactic therapy for prevention of venous thromboembolism during surgery has been well established in the medical literature.³⁶ However, determining an appropriate therapeutic program for venous thromboembolism prevention remains confusing for many surgical practitioners, especially when the surgical procedure is deemed “minor”, the duration of surgery is deemed short, and the patient is discharged home after recovery from surgery and anesthesia.

Nonpharmacologic therapy (compressive hose and intermittent pneumatic compression of the foot/leg) may reduce the risk of deep venous thrombosis (DVT) by up to 60%.³⁵ Pharmacologic therapies for prevention of perioperative DVT has been shown to be more effective than mechanical therapies alone but increases the risk of major bleeding complications from surgery. The use of both mechanical and pharmacologic therapy for prevention of perioperative DVT has not been shown to add additional protective benefit over pharmacologic therapy alone.³⁵ Combined use of both compressive hose and pneumatic compressive devices has not been shown to reduce the incidence of DVT over compressive devices used alone. Elastic stockings causing skin complications in some patients are of concern. The duration of use of pharmacologic therapy for the prevention of DVT will be based on specific patient needs. The use of an inferior vena-caval filter as a *primary* prophylaxis modality is generally not recommended but may be appropriate for patients having a pulmonary embolism in the postoperative period. The primary concern with chemoprophylaxis for venous thromboembolism prevention is postoperative bleeding, particularly after facial cosmetic surgery, surgery that may affect patency of the airway, and liposuction where large areas of tissue have been disrupted and blood collection may be extensive. As a result of these concerns, prophylactic therapy for ambulatory plastic surgery has focused on the use of graduated compression stockings (compressive hose) and the use of intermittent pneumatic compression devices fitted for the foot/leg. The use of these techniques has been shown to reduce the incidence of venous thromboembolism.³⁷ It remains to be demonstrated whether these nonpharmacologic techniques prevent pulmonary embolism or death following outpatient plastic surgery. Compressive hose must be properly fitted for them to be effective, and ill-fitted stockings may lead to venous occlusion or arterial compromise of the lower extremity.

The use of intermittent pneumatic compressive devices for the leg or foot increases venous flow and is thought to reduce pooling of blood in the veins. Once again, proper fitting of the device is mandatory and use of the pneumatic compressive device should start before beginning anesthesia and continue through the recovery period in the postanesthesia care unit. The development of venous thromboembolism may extend well into the postoperative period following discharge from the medical care facility. In selected cases it may be wise to continue mechanical prophylaxis at home, after discharge from surgery, for the high-risk patient. Patients who have undergone circumferential liposuction of the thigh or calf, where the venous flow of the lower extremity may be compromised, may benefit from extending the duration of mechanical

prophylaxis. Mechanical prophylaxis is contraindicated in patients with lower-extremity edema, a history of peripheral vascular disease of the lower extremity, or wounds or ulcers of the feet or legs.

Patients at high risk for venous thromboembolism include those with a history of prior venous disease, obesity (body mass index >30), postoperative immobility, diabetes, history of tobacco use, history of cancer, advanced age, long duration of surgery, and the use of general anesthesia.³⁸ This subset of high-risk patients may benefit from a combination of mechanical and pharmacologic prophylactic measures to reduce the incidence of venous thromboembolism. Patients who are thought to be hypercoagulable (e.g., protein S deficiency or factor V Leiden) may also warrant both mechanical and pharmacologic therapy for thromboprophylaxis during outpatient ambulatory surgery.³⁹ Pharmacologic prophylaxis is contraindicated in patients with active bleeding, recent or anticipated regional anesthesia (epidural or spinal), infective endocarditis, proliferative retinopathy, and in patients with thrombocytopenia. Patients undergoing surgery with epidural anesthetics and the use of an indwelling epidural catheter should have the catheter removed before starting anticoagulant therapy. In patients with an indwelling catheter in whom anticoagulation therapy has been instituted, the catheter should be removed at the low point of clinical effectiveness of anticoagulation therapy; that is, just before the administration of the next dose of medication. The international normalized ratio should be <1.5 at the time of catheter removal. The use of heparin and low-molecular-weight heparin is contraindicated in patients with a history of heparin-induced thrombocytopenia. Fondaparinux may be an appropriate prophylactic therapy for patients with heparin-induced thrombocytopenia. Aspirin as a sole modality for venous thrombosis prophylaxis is generally not recommended. Aspirin may be indicated in a small subset of patients at high risk for venous thrombosis and with specific contraindications for other mechanical and pharmacologic therapies.

Intermittent pneumatic compression devices are routinely used for all liposuction patients because of concern with venous stasis, vascular endothelial injury, and/or activation of the coagulation pathway secondary to tissue trauma during surgery. Anticoagulation therapies started prior to or immediately following liposuction surgery pose substantial bleeding risk to the patient. During liposuction, large areas of tissue are disrupted during surgery and visualization of bleeding sites may be difficult. Patients who develop pulmonary thromboemboli in the early postoperative period and given aggressive anticoagulant therapy have experienced a great amount of bleeding in the body areas having liposuction. Anticoagulated liposuction patients will experience severe bleeding, even with aggressive compressive garment therapy in the regions of recent surgery. Vena-caval filters have been successfully placed in postliposuction patients experiencing pulmonary emboli. For postliposuction patients experiencing these life-threatening complications, consultation with critical care medicine and vascular surgery specialists is mandatory.

The development of a formal, institutional policy for prevention of DVT and thromboembolism is recommended. Compliance with institutional policy should also be monitored to ensure patients are receiving appropriate DVT prophylaxis therapy.

Care of the liposuction patient during surgery

Coordination of patient care during liposuction by the operating team is mandatory. Strategies for tumescent solution dosing, fluid management, patient positioning, and maintenance of the patient's body temperature during surgery should be planned prior to the start of the surgical procedure. Liposuction patients frequently have large portions of their body surface area exposed to cold operating room temperatures. Maintaining body temperature for the patient during surgery may become a complex problem for the surgical team. Anesthetics routinely cause blood flow redistribution, antagonizing the body's normal mechanisms for temperature regulation. Warmed intravenous fluids and tumescent solutions for liposuction will aid in temperature preservation. Water-based operating table heating pads have been shown to have little benefit for temperature preservation. Routine use of two forced air heating blankets, one over the upper part of the body and the second over the lower part of the body, have almost eliminated concern over hypothermia during liposuction. Changes in body positioning during liposuction surgery must be performed expeditiously, with reapplication of the forced air blankets as soon as is possible to maintain body temperature.

The most common postoperative complication after liposuction is skin and body contour irregularity. Of course, the most serious outcome after liposuction is death. Abdominal wall and vital organ perforation has been reported to occur in 14.6% of 95 fatalities following 496,245 liposuction procedures.⁴⁰ Patients with previous abdominal surgery or known to have a ventral hernia appear to be at increased risk of abdominal wall perforation. Careful preoperative abdominal examination will identify many patients with abdominal wall hernias. Advanced imaging by computed tomography scan may be necessary to help identify patients with abdominal wall defects that could lead to severe complications after abdominal liposuction. Meticulous surgical technique is required to reduce the incidence of vital organ injury. Perforation of the posterior flank, leading to retroperitoneal injury, thoracic perforation, and spinal cord injury, has been reported during liposuction. Delay in diagnosis of an abdominal wall perforation may lead to peritoneal spillage, necrotizing fasciitis, sepsis, and death.⁴¹ The only thing worse than such a catastrophic complication is the failure to diagnose such a condition. Physician denial that a complication has occurred is a strong component in the pathway leading to a devastating clinical outcome after surgery.

Complications during body contour surgery: fat transfer

The addition of fat transfer techniques has expanded the possibilities associated with body contour surgery. Prior to the development of fat transfer from one part of the body to another, body contour changes focused on fat removal (liposuction). The removal of fat from a donor source on the body combined with adipose cell processing and subsequent transfer to another part of the body has increased patient demand

for the procedure. With development of the transfer technique comes the possibility of intravascular injection of fat tissue and adipose cells leading to complications and death. Fat emboli as a complication of liposuction has been reported in the medical literature. Inadvertent intravascular injection of fat tissue has been reported during fat transfer to the buttocks.⁴² Microembolization of fat particles and large fat globules into the pulmonary vasculature has been reported. Fat transfer to the buttock may be performed by transfer of fat tissue to the subcutaneous/adipose region of the buttock or by transfer of fat tissue into the gluteal muscles of the buttock. Intramuscular transfer of fat tissue to the deeper muscular layers may increase the risk of intravascular injection to the deep venous plexus underneath the muscle layers. Inadvertent, deep intravascular injection into the iliac vessels has also been proposed as a mechanism for fat embolism to the lung. Determining the appropriate depth of tissue transfer to the buttocks may be difficult. Identifying the vascular structures deep within the buttocks with intraoperative ultrasound to avoid vascular injection has been proposed but remains an untested technique. Aspiration by syringe prior to injection of tissue may help avoid vascular injection of tissue but is unlikely to completely eliminate a potentially life-threatening complication. Deep needle penetration to the buttocks also raises the possibility of sciatic nerve injury when anatomical landmarks are distorted.

Embolization of tissue filler materials, including fat transfer, following injection into the face resulting in blindness has also been reported. It has been suggested that intravascular injection resulting in retrograde flow and embolization of the retinal artery is the cause of these unfortunate complications. Again, careful surgical technique may reduce the incidence of embolization. Careful aspiration prior to injection, and use of small-diameter, blunt-tipped needles may reduce the incidence of intravascular injection as compared to sharp, pointed tip needles.⁴³

Facial aesthetic surgery

Hematoma formation after facial rejuvenation surgery can have serious consequences. Small hematomas may be treated with conservative techniques, such as external pressure to the affected area, or require percutaneous aspiration with a needle and syringe. Large hematomas, expanding hematomas, or blood collections causing pressure on the patient's airway are more likely to require surgical intervention. Surgical studies have identified perioperative hypertension with systolic blood pressure greater than 150 mmHg and diastolic blood pressure greater than 90 mmHg as a prime marker for postoperative hematoma formation after facial surgery. Recommendations for aggressive blood pressure control surrounding the time of planned rhytidectomy have been proposed by many authors. Whether preoperative prescription of antihypertensive medications such as clonidine should be used to reduce the incidence of postoperative facial hematoma, as opposed to intraoperative titration of antihypertensive medications, is as yet unanswered. As with any such critical question, randomized studies will need to be performed. The administration of oral or intramuscular medications around the time of surgery should be carefully evaluated. The perioperative use of Thorazine® to control intraoperative and

postoperative blood pressure during rhytidectomy needs to be questioned. Thorazine® has a long half-life and a long clinical duration of action. It has numerous undesired drug interactions, including potentiation of narcotic analgesics, and a variety of side effects. Given that we now have better, titratable antihypertensive medications, more potent antiemetics, and better perioperative sedative medications, Thorazine® in the surgical setting is a drug best relegated to history.

Airway management of the patient with a postoperative facial hematoma may be frightening. Facial and neck hematomas may significantly distort the airway making direct laryngoscopy and intubation impossible. Careful evaluation of the patient's airway and anatomy distortion should be performed prior to administration of sedative medications or induction of general anesthesia in a patient with facial or neck hematoma. Deviation of the trachea by a neck hematoma or swelling of the base of the tongue or pharynx can cause airway obstruction. Traditional airway rescue techniques such as the laryngeal mask airway may not be effective because of anatomical distortions caused by the hematoma. Securing the airway with an endotracheal tube with the patient awake and spontaneously breathing may be the safest technique prior to induction of general anesthesia in patients with distorted anatomy from a postoperative hematoma. Opening a suture line with evacuation of a small area of hematoma may relieve pressure on the airway and restore a more normal airway anatomy. In this clinical setting, preparations should be made for performing a surgical airway prior to attempts at fiberoptic or awake intubation. Preparation for an airway crisis will help avoid a clinical disaster should airway complications develop. Massive neck swelling may also make performance of a surgical airway or cricoid thyroidotomy difficult.

Evacuation of a small postoperative facial hematoma after rhytidectomy may be an appropriate procedure for an office-based surgery center or free-standing surgery center. In a case with possible airway compromise following facial surgery, a hospital-based operating facility may provide the greatest level of safety for the patient. It may be necessary for the patient to remain intubated after hematoma evacuation because of continued swelling in the neck, pharynx, and base of tongue. Again, preparation for rapid deterioration of the patient's airway is mandatory.

Complications from breast surgery

The incidence of pneumothorax following breast augmentation and breast reconstructive surgery is very low – less than 1% of cases. The incidence of a pneumothorax following primary breast augmentation is fortunately very rare, but must be considered in a patient with otherwise unexplained postoperative respiratory complications. Pneumothorax after secondary breast surgery and breast reconstruction has been reported at a higher incidence but remains infrequent. Severe postoperative respiratory distress after breast surgery may require positive-pressure respiratory assistance and intubation along with needle aspiration of the chest for evacuation of a pneumothorax. Chest tube insertion for continued management of a pneumothorax is rare, but may be required for a persistent air leak. Keeping this potential complication in mind will allow recognition of the disorder when it presents itself clinically.

Fire in the operating room

The development of thermal injury secondary to a fire in the surgical field can lead to devastating consequences. As many as 200 operating room fires involving patients undergoing surgery may be occurring every year. The concept of the fire triad helps to explain the development of a fire during surgery. The fire triad comprises: (1) an oxidizer, which in an operating room setting includes oxygen and nitrous oxide; (2) an ignition source, which may be an electrocautery-type device or laser; and (3) a fuel source such as drapes, gauze, prepping solutions, or a patient's body tissue. Prevention of fires in the operating room during surgery starts with physician and staff awareness of the possible contributing factors to an operating room fire. The ASA Taskforce on Operating Room Fires has developed specific recommendations to reduce the incidence of operating room fires.⁴⁴ Oxygen-enriched environments readily promote ignition of a combustible material. The contour of the surgical drapes around the patient's face may allow oxygen to accumulate and promote combustion. Allowing free air flow around a surgical area may reduce the incidence of ignition of combustible material. Minimizing the delivery of supplemental oxygen (nasal cannula or face mask) to the surgical region may reduce the incidence of combustion. For patients receiving supplemental oxygen via nasal cannula or face mask while undergoing facial surgery, minimizing the oxygen concentration in the surgical field is mandatory. This may be achieved by using the lowest possible oxygen flow to the patient that produces satisfactory oxygen saturation levels, and by suctioning in the surgical field to reduce oxygen accumulation in the surgical area. It may be necessary to secure the airway for high concentration of oxygen delivery to the patient to reduce the risk of fire of the face or airway.

Surgical sponges should be moistened when used near an ignition source. Flammable skin-prepping solutions should be allowed to dry before draping to reduce the risk of accumulation of potentially flammable gases. The lowest possible cautery and laser settings should be used to limit ignition potential. Treatment of a facial or airway fire includes stopping the flow of delivered gases to the patient, removal of burning material as soon as possible, including an enflamed endotracheal tube if it has caught on fire, and extinguishing flames with saline as rapidly as possible. Concerns with airway thermal injury must be thoroughly evaluated with laryngoscopy and bronchoscopy if necessary. Airway management after facial fire or airway thermal injury will require additional medical consultation and intensive care unit monitoring of the patient.

Protocol-based systems for reducing wrong patient and wrong-sided surgery

Much of this chapter has discussed techniques for improving patient safety during surgery based on our knowledge of the pharmacology and physiology of the surgery being performed. Other portions of the chapter have sought to educate the medical practitioner through review of the medical literature of surgical and anesthetic risk. Other portions of this textbook seek to educate the medical practitioner on surgical

technique and improving clinical outcome through better surgery. Most physicians strive to improve clinical outcome by advancing their knowledge of the scientific literature that is the basis of medical practice. However, poor patient outcome during surgery is often due to failure of the medical system to meet the needs of the patient. Medical facilities should have mechanisms in place to ensure that patients receive the correct surgical procedure. Following this concept, the Joint Commission under the National Patient Safety Goals has adopted the Universal Protocol for Preventing Wrong Site, Wrong Procedure and Wrong Person Surgery.⁴⁵ The Universal Protocol is founded on the concept that performing the wrong surgery must be prevented and that aggressive strategies must be implemented for successfully protecting the patient. Verification of patient identity is performed multiple times by multiple individuals involved in the medical care and surgical care process. This verification process begins with preoperative patient verification and confirmation of medical conditions. This preoperative verification includes patient identity confirmed verbally with the patient and with checking the patient's arm band. Confirmation of the surgical site and surgical procedure along with proper surgical site marking by the physician or designee is performed. Verification of the surgical permit, appropriate history, and physical examination documentation along with laboratory studies and plans for blood transfusion are included in this preoperative review. Which members of the surgical team should be allowed to perform surgical site marking remains highly controversial in the medical community. These debates will continue, but it is safe to state that the surgical site must be marked preoperatively, meeting the National Patient Safety Goals and good perioperative medical judgment.

The World Health Organization has adopted a surgical patient safety checklist to reduce the incidence of medical errors.⁴⁶ This checklist includes procedures to be performed prior to the induction of anesthesia (Boxes 8.1 & 8.2).

Performance of the "time-out" procedure ensures that the correct patient is about to undergo the correct surgery on the correct surgical site. The "time-out" procedure requires that the entire operative team focus on the identification process and participate in performing the "time-out." The operative team includes the surgeon and surgical assistants, the anesthesia care provider, the nurse in the operating room, the surgical technician, and other individuals in the operating room who will be participating in the surgical procedure (i.e., radiology personnel). When more than one procedure is to

BOX 8.1 Confirm the following information with the patient prior to induction of anesthesia

- Patient identity
- Site marking by surgeon
- Surgical consent
- Current history and physical
- Allergy band
- Special needs or instrumentation, i.e., continuous positive airway pressure machine for after surgery for a patient with sleep apnea

BOX 8.2 Confirm with anesthesia care provider

Anesthesia safety check completed
 Pulse oximeter in place and functioning
 Anticipated difficult airway or pulmonary aspiration risk
 Risk of blood loss greater than 500 cc in an adult or greater than 7 mL/kg in a child
 Need for blood typing and crossmatch
 Special anesthesia equipment needs

be performed on the same patient by different surgeons, a “time-out” is performed before the start of each portion of the surgery. The “time-out” procedure must confirm:

1. The patient’s identity is correct.
2. The surgical site is correct.
3. The surgical procedure that is planned.
4. Surgical consent is complete and accurate.
5. The surgical site has been properly marked and is visible in the surgical field.
6. Imaging studies and implantable devices are available (if indicated).
7. Prophylactic antibiotics (if indicated) have been given.
8. Deep venous thrombosis prophylaxis has been instituted (if indicated).
9. Implementation of aseptic technique has been reviewed.
10. Procedure duration and anticipated blood loss are checked.
11. Other areas of concern during surgery by any member of the surgical team are noted.

After completion of the procedure a postsurgical evaluation is performed by the surgical team. This portion of the surgical safety checklist includes:

1. Sponge and needle counts are correct.
2. Review of the surgical consent confirms completion of all planned procedures.
3. Pathology specimens will be properly sent to the lab.
4. Plans for postanesthesia recovery have been made and personnel have been notified of the patient’s forthcoming arrival.

All team members must be full participants in the “time-out” procedure. Failure to perform these well-established procedures puts the patient at risk for grave error and brings into question the quality of care being provided to the patient.

The sociology of the plastic surgery operating room

The American Society of Plastic Surgery and the American Society for Aesthetic Plastic Surgery have promoted a “patient-first” initiative in advocating for safety in the operating room. Advances in surgical technique and perioperative medical management have allowed improved clinical outcomes. As much as our medical knowledge increases, we sense a great disappointment when the clinical outcome is not as good

as expected. Attempts at regulation of the surgical environment, with accreditation of surgical facilities, have certainly increased the quality of documentation during surgery, but have they improved outcome? Accreditation of a surgical facility includes reviewing processes and systems but may not actually observe the performance of a single surgery. The accreditation process taking 1, 2, or 3 days evaluates a surgical facility at a point in time. The actual conduct of that facility going forward may not come under scrutiny for another 1–3 years. Compromise in standards by a physician or by the surgical facility may occur slowly and yet soon be so substandard as to put the patient at unnecessary risk. Ultimately, the decision to practice plastic surgery safely will rest with the physician.

The standard of clinical practice in a surgery center or office-based surgical facility must meet or exceed that of an accredited hospital. A series of 10 core principles was published in 2004 advocating the fundamentals of practice for aesthetic surgery.⁴⁷ These same principles are as valid today as when they were first published and should apply to all practitioners and all surgical specialists. Patients should be selected for surgery based on the established criteria set by the ASA classification system. Physicians performing office-based surgery must have admitting privileges at a nearby hospital and a transfer agreement with that hospital facilitating patient transfer and admission when needed. Physicians performing office-based surgery must show competency by maintaining surgical privileges at an accredited licensed hospital or ambulatory surgery center for the same procedures being performed in the office setting. Serious peer review of surgical performance and medical management in an outpatient surgical center or a private surgical facility should be mandatory for the benefit of the patient. Is it appropriate that a physician who is denied privileges at a hospital to perform surgery has the right to open a private facility without peer review and perform those same procedures? Should a privately owned surgical facility function as a hiding place for a physician to escape peer review? The same rules that apply to a practicing surgeon should also apply to the practicing anesthesiologist. No medical practitioner should be above answering to his or her medical peers during a clinical review.

We must begin to question the conduct of clinical practice in the operating room during surgery. A patient can reasonably expect that the focus of the surgical team will be dedicated to performing their jobs to deliver the best possible surgical outcome. Surgical team members (nurses, scrub technicians) who have gone through great effort to maximize the quality and safety of the surgical outcome are not interchangeable with other individuals who have not familiarized themselves with the medical facts of the case. The risk for error increases and the quality of care for the patient decreases when surgical team members change during surgery. No matter how complete the medical “handoff” from one team member to another, no handoff can be as complete as having been in the case from the beginning. Having several different operating room nurses and surgical technicians during a single surgery increases the risk of error and should be discouraged. Continuity of care by the anesthesia care team also improves patient safety. Plastic surgery cases may take a long time and some change in personnel may be necessary during the procedure, but should be minimized. It should not need to be said, but surgery should be performed by the attending surgeon

and designated assistants and not by unlicensed minimally trained individuals deemed “qualified” by the surgeon. A lack of operating room oversight can lead to poor practice quality that may not be detected by a chart and documentation review by a certifying agency.

Best of intentions, not the best of results

Despite the best of intentions on the part of physicians and the healthcare system, errors occurring during hospitalization may cause upwards of 98 000 deaths per year and over 1

million significant injuries. Recent publication of a study showing a failure of new hospital policy and procedures to improve patient safety in a hospital setting is disappointing. Chart review of 2341 randomly selected hospital admissions from 10 randomly selected hospitals between 2002 and 2007 was performed.⁴⁸ In this review, patients were deemed to have been harmed during their hospitalization in 588 instances, about 1 in 4 patients. In 50 of these cases the harm was considered to have been life-threatening, 17 cases resulted in permanent injury and 14 deaths were deemed in part due to medical error. Despite implementation during the study period of policies and procedures to reduce medical error, the error rate remained steady at 25 harms per 100 hospital admissions.⁴⁹



Access the complete reference list online at <http://www.expertconsult.com>

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Anesthesia and pain management in plastic surgery

Paul N. Afrooz and Franklyn P. Cladis

SYNOPSIS

- Inadequate pain control may decrease quality of life and delay recovery and the return to normal activities.
- NSAIDs are very efficacious and have a low NNT (number needed to treat).
- Obstructive sleep apnea (OSA) increases opioid sensitivity and appears to increase the risk for postoperative respiratory complications.
- Regional analgesia (epidural, paravertebral, transversus abdominis plane block) reduces postoperative opioid requirements.

Introduction

Pain management before, during, and after any procedure is a key component to successful outcomes in plastic surgery. Consistent patient satisfaction hinges largely upon favorable impressions and recollections of the surgical experience. As such, patient satisfaction and pain management protocols must be effective, dynamic, multimodal, and customizable.

Pain is a self-reported, complex, and subjective experience commonly defined as an unpleasant sensory and emotional experience due to actual or potential tissue damage.¹ The perception of pain involves both the peripheral and central nervous system. Both spinal and supraspinal sites play a role in the perception of pain within the central nervous system. Pain can be generally classified into physiological and pathological pain. Physiologic or nociceptive pain is acute in nature and serves as a warning or protective function, thus promoting healing and rendering it physiologically useful. In contrast, chronic pain (e.g., neuropathic) persists beyond the period of healing rendering it nonprotective and maladaptive; otherwise classified as pathologic pain.

Historically, pain protocols have relied heavily on opioid-based therapies which have several inherent drawbacks. The etiology of pain is often multifactorial, and therefore successful treatment depends on a multimodal approach. Analgesic regimens should target the peripheral nociceptors at the site

of tissue injury, peripheral nerves supplying the surgical area, and both spinal and supraspinal sites. This multi-targeted strategy provides highly effective pain management while minimizing the adverse effects of single-agent strategies.

This chapter will focus on current concepts in pain management in plastic surgery while drawing on several themes, including:

- Multimodal analgesia with an emphasis on opioid reduction
- Neuraxial analgesia such as epidural, paravertebral, and peripheral nerve blocks
- Field blocks
- Systematic extensive surgical site infiltration with long-acting local anesthetics.

Clinical consequences of inadequate pain relief

Despite new strategies and evolving pain management regimens, postoperative pain remains one of the primary concerns of patients undergoing surgery. Approximately 80% of patients report acute pain after surgery with the majority experiencing moderate-to-severe pain.² The clinical manifestations of inadequate pain management include myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, and anxiety (Table 9.1).^{3,4}

Inadequate management of postoperative pain also results in significant increases in healthcare costs by way of prolonged post-anesthesia care unit stay, delayed discharge, and readmission.⁵⁻⁸ Furthermore, inadequate pain control may decrease quality of life and delay recovery and the return to normal activities.⁹

The clinical impact of inadequate pain control in the perioperative period is significant, casting an array of effects on multiple organ systems. The potential for postoperative wound infections is particularly concerning in plastic surgery. Surgical stress induces an inflammatory reaction and the release of a

Table 9.1 Consequences of unrelieved pain

Cardiovascular	Increased heart rate, peripheral vascular resistance, arterial blood pressure, and myocardial contractility, resulting in increased cardiac work, myocardial ischemia, and infarction
Pulmonary	Respiratory and abdominal muscle spasm (splinting), diaphragmatic dysfunction, decreased vital capacity, impaired ventilation and ability to cough, atelectasis, increased ventilation/perfusion mismatch, hypoventilation, hypoxemia, hypercarbia, increased postoperative pulmonary infection
Gastrointestinal	Increased gastrointestinal secretions and smooth muscle sphincter tone, reduced intestinal motility, ileus, nausea, and vomiting
Renal	Oliguria, increased urinary sphincter tone, urinary retention
Coagulation	Increased platelet aggregation, venostasis, increased deep vein thrombosis, thromboembolism
Immunologic	Impaired immune function, increased infection, tumor spread or recurrence
Muscular	Muscle weakness, limitation of movement, muscle atrophy, fatigue
Psychological	Anxiety, fear, anger, depression, reduced patient satisfaction
Overall recovery	Delayed recovery, increased need for hospitalization, delayed return to normal daily living, increased healthcare resource utilization, increased healthcare costs

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number of humoral mediators along with increased levels of cortisol during surgery. Together, these substances can have detrimental systemic effects including hyperglycemia, catabolism, impaired immune function and wound healing.^{4,10–12} This physiologic and sometimes detrimental stress response to surgery may be mitigated through adequate analgesia.

Acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 selective inhibitors

Historically, opioids have been used successfully for pain management in plastic surgery procedures; however, their side-effect profile limits routine use, particularly in ambulatory procedures. For those procedures that do not involve surgical manipulation of major muscle groups or osteotomies, pain management can usually be fulfilled with non-opioid medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and local anesthetics.¹³ The advent of cyclooxygenase (COX)-2 selective inhibitors (coxibs), as well as drugs such as gabapentin/pregabalin, clonidine, and low-dose ketamine have added new dimensions in the armamentarium of plastic surgery procedures. See [Table 9.2](#) for dosing.

Acetaminophen

Though less potent than NSAIDs or coxibs, acetaminophen is the most frequently prescribed analgesic for the treatment of acute pain. It is often preferred because it is well tolerated. Despite the similarities to NSAIDs, the precise mechanism of action of acetaminophen is unclear. It is believed to act via inhibition of COX-1 and COX-2 enzymes through metabolism by the peroxidase functions of these enzymes both centrally and peripherally. Additional peripheral effects may be attributable to inhibition of isoforms of COX-1, COX-2, and COX-3 enzymes involved in prostaglandin synthesis, thereby

increasing the pain threshold.^{13,14} Acetaminophen is available in oral, rectal, and IV formulations, and is both analgesic and antipyretic at therapeutic doses with a dose-dependent efficacy. The maximum recommended *daily* dose in adults without hepatic or renal disease is 4 grams with dose reduction recommended in patients with liver insufficiency.

IV acetaminophen produces a rapid and predictable plasma concentration, and is recommended as a first-line agent for the treatment of pain and fever in adults and children if oral administration is not possible.¹³ The analgesic efficacy of acetaminophen has been demonstrated in double-blind clinical trials. Single dose or multiple doses of IV acetaminophen (1 g) were significantly greater than placebo in adult patients who had undergone dental, orthopedic, or gynecologic surgery.

When used in therapeutic doses, acetaminophen is a relatively safe drug with few and mild side effects. In comparison to opioids, there is no effect on respiratory drive, and furthermore, it does not cause sedation, nausea and vomiting or reduced gastrointestinal motility. In addition, the effects on platelets and hemostasis are insignificant in patients without a history of coagulopathy.¹⁵ There are no significant cardiovascular, renal, or pulmonary side effects. The most significant side effect is hepatotoxicity when administered in high doses, chronic use, or when administered with alcohol or other various hepatotoxic drugs. Very rare side effects include blood dyscrasia (i.e. thrombocytopenia), methemoglobinemia, and hemolytic anemia.

Nonsteroidal anti-inflammatory drugs

NSAIDs have been used effectively for the treatment of acute and chronic pain for several decades. The primary mechanism of action is through the inhibition of both COX-1 and COX-2 enzymes, thereby inhibiting the synthesis of thromboxanes and prostaglandins. NSAIDs have well-established analgesic, antipyretic and anti-inflammatory properties. Pharmacokinetic data and selectivity of action are shown in [Tables 9.3](#) and [9.4](#).¹³

Table 9.2 Acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase (COX)-2 selective inhibitors dosing

Generic name	Brand name (®)	Dose (mg/kg) Frequency	Maximum ADULT daily dose (mg)	Comments
Acetaminophen (paracetamol)	Tylenol®, Panadol® Ofirmev®	10–15 PO q 4 h (1000 mg, max) 15 IV q 6 h (1000 mg, max)	4000	Lacks anti-inflammatory activity No platelet effects Hepatic failure with overdose
Acetylsalicylic acid (aspirin)	Bayer®, Bufferin®, Anacin®	10–15 PO q 4 h	4000	Inhibits platelet aggregation GI irritability
Ibuprofen	Motrin®, Advil®	5–10 PO, IV q 6–8 h (400–800 mg)	3200	Available as an oral suspension Renal dysfunction GI irritability Inhibits platelet aggregation
Naproxen	Naprosyn®	5–10 PO q 12 h	1500	See Ibuprofen
Ketorolac	Toradol®	IV or IM Load 15–30 mg Maintenance 15 mg q 6 h	120	May be given orally Maximum dose 30 mg Can cause GI upset and ulcers Discontinue after 5 days
Celecoxib	Celebrex®	>25 kg: 100–200 mg (<u>total dose, not mg/kg</u>) PO BID	400	Selective COX-2 inhibitor Less GI distress, less anti-platelet effect Risk of MI in adults with chronic administration

Generally, NSAIDs are very efficacious and have a low NNT (number needed to treat) when used in appropriate doses. Data supports the use of NSAIDs for acute pain management following a variety of ambulatory surgical procedures including plastic and aesthetic surgery. Through a series of meta-analyses, the Cochrane group has demonstrated the analgesic efficacy and safety of single dose NSAIDs, ketoprofen, ketorolac and lornoxicam.^{16,17}

NSAID hypersensitivity as well as cross-reactivity between different drugs have been reported. In patients with a reported history of sensitivity to acetylsalicylic acid, administration of

NSAIDs should proceed with caution. Coxibs may provide a safer alternative; however, cross-reactivity and hypersensitivity in those allergic to NSAIDs is not guaranteed.¹⁸ Celecoxib has a similar structure to sulfonamides and should not be given to patients with a known sulfa drug allergy. NSAIDs are known to cause GI irritation, and GI bleeding. Platelet function is affected, which often results in impaired hemostasis. Furthermore, as a result of prostaglandin inhibition, NSAIDs pose a potential risk for renal insufficiency. Renal insufficiency occurs specifically in the presence of hypovolemia mostly due to perioperative bleeding or dehydration.

Table 9.3 Pharmacokinetic data of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase (COX)-2 selective inhibitors

Drug	Bioavailability	Peak plasma concentration	Plasma half-life	Duration of action
Acetaminophen oral (1 g)	85–95%	10–90 min	2–3 h	4–6 h
Acetaminophen IV (1 g)	100%	5–10 min	2.7 h	4–6 h
NSAID				
Indomethacin (50 mg)	90%	1 h	4.5 h	4–6 h
Ibuprofen (400 mg)	?	1–2 h	2 h	4–6 h
Diclofenac (50 mg)	60–70 %	15–30 min	1.2–2 h	4–8 h
Ketorolac IV (30 mg)	100%	10–15 min	4–9 h	11 h
COX-2 inhibitors				
Etoricoxib (120 mg)	100%	1 h	22 h	20 h
Part-coxib IV (40 mg)	100%	10–15 min	8 h	15 h

Data are presented as average values (data obtained from different sources)

From Gupta A, Jakobsson J. Acetaminophen, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 selective inhibitors: an update. *Plast Reconstr Surg.* 2014;134(4 Suppl 2):24S–31S.

Table 9.4 The selectivity of different NSAID and COX-2 inhibitors on the COX-2 and COX-1 isoenzymes

Drug	COX-2/ COX-1 ratio	COX-1/ COX-2 ratio
Aspirin	167	3.1
Naproxen	0.6	1.7
Ketorolac	2	0.5
Diclofenac	2.2	1.4
Indomethacin	30	0.02
Ibuprofen	15	0.007
Piroxicam	33	0.04
Tenoxicam	15	0.62
Meloxicam	0.33	3
Etoricoxib	0.02	344
Celecoxib	0.03	30
Rofecoxib	0.003	272

Cardiovascular side effects include myocardial infarction, particularly with underlying ischemic heart disease. This side effect differs between drugs, with diclofenac posing the greatest risk, and naproxen the least.

Contraindications for NSAIDs, both relative and absolute, are numerous, and discretion must be used in patients with comorbid conditions. However, they remain very effective adjuncts to perioperative pain management. Their routine use in plastic surgery procedures may be precluded due to the minor increase in risk of bleeding and hematoma.¹³

COX-2 receptor inhibitors

Selective COX-2 inhibitors were developed in an effort to reduce the GI side effects and bleeding associated with NSAIDs. Coxibs reduce but do not eliminate the risk for GI bleeding. They are effective in the management of postoperative pain and have a low NNT, but their analgesic effect has not been proven to be superior to traditional NSAIDs. A major advantage of coxibs is their negligible effect on platelet function. The risk of bleeding or hematoma formation is negligible.^{13,19}

The long-term use of coxibs is associated with potential risk for cardiovascular and thromboembolic events. Due to the risk of perioperative myocardial infarction, coxibs should be avoided in patients with ischemic heart disease. There is no difference in the incidence of renal side effects between NSAIDs and coxibs. Overall, coxibs have a lower risk for bleeding complications due to a negligible effect on platelet function, and a lower risk of GI ulcers and bleeding compared to NSAIDs.¹³

Acetaminophen, NSAIDs, and coxibs are effective agents in multimodal perioperative pain management. Acetaminophen has minimal effect on platelet function and can be used safely without any such risk for bleeding or hematoma. It can be administered intravenously, and can reduce the need for opioid analgesics. NSAIDs and coxibs are effective analgesics and demonstrate an additive effect when combined with acetaminophen. While NSAIDs affect platelet function and

increase the risk for bleeding and hematoma, coxibs have minimal risk for bleeding and hematoma formation as well as a lower risk for GI side effects and better tolerance in asthmatics. However, the risk for thromboembolic side effects prevents their use in patients with ischemic heart disease or a history of thrombotic events. Acetaminophen and NSAID/coxib agents in the perioperative period are well established in clinical practice. The exact regimen can be tailored for each individual patient based on risk/side-effect profile of these agents. In combination with other non-opioid analgesics, these drugs can be very effective in pain management in plastic surgery.¹³

Opioids

Opioids are proven to be effective, reliable, and easily titrated in the perioperative period. Current formulations are derived from natural and synthetic sources, and prescriptions of this class of medication are strictly controlled by the Drug Enforcement Agency of the United States. Opioids act mainly on opioid receptors in the spinal cord, medulla and cerebral cortex modifying ascending pain signals and altering the perception of pain. The bound opioid receptors are also responsible for the adverse effects including constipation, sedation, and pruritus.²⁰

In an acute analgesic regimen, opioids may be administered orally or parenterally. Rapidity of onset and predictable plasma levels are advantages of parenteral administration, though disadvantages of IV injection include rapid rise in plasma concentration, and the need for skilled provider administration and observation. Patient-controlled analgesia (PCA) is a modality of delivering opioids that may improve analgesia and patient satisfaction and reduce side effects by decreasing total exposure. It has gained popularity due to an increased safety margin, ease of administration, increased efficacy of analgesia, and decreased provider workload.²⁰ See Table 9.5 for dosing. PCA dosing recommendations are outlined in Table 9.6. These doses may need to be reduced further in patients who are at risk of opioid sensitivity (obesity, obstructive sleep apnea, elderly).

Serious side effects are seen with opioid administration including addiction, as illustrated by nearly 15000 prescription opioid-related overdose deaths in 2008.^{20,21} A significantly increased risk of road trauma is seen with increasing opioid dose.²² Chronic opioid therapy is also associated with a dose-dependent increase in the severity of sleep-disordered breathing.²³ Furthermore, even short periods of exposure to opioids are associated with the risk of opioid tolerance and hyperalgesia which can potentially lead to chronic pain.^{24,25}

Avoiding adverse effects associated with opioids requires implementation strategies for decreasing total opioid doses while maintaining adequate analgesia. Adjuvant medications as well as surgical anesthetic techniques are paramount to dose reduction. Opioids prescribed in the immediate postoperative period should be emphasized as a short-term regimen with transition to non-opioids as soon as appropriate.²⁰ Risk reduction strategies are shown in Table 9.7.

Specific patient populations may be at increased risk for adverse effects with opioid therapy. These include patients with obstructive sleep apnea (OSA) and obesity, elderly patients, and patients on chronic opioid therapy. Obese

Table 9.5 Opioid dosing

Agonist	Equipotent IV dose (mg/kg)	Equipotent PO dose (mg/kg)	Duration (hr)	Oral bioavailability (%)	Comments
Morphine	0.1 (2–4 mg every 2–4 hrs PRN)	0.3	3–4	20–40	“Gold standard”, very inexpensive Histamine release, vasodilation, consider avoiding in asthmatics and in circulatory compromise Poor oral bioavailability; give 3–5 times the IV dose
Meperidine (Demerol®)	1	N/A	3–4	60–80	Catastrophic interactions with MAO inhibitors Tachycardia; negative inotrope Metabolite normeperidine produces seizures 12.5 mg effectively treats shivering Not recommended for routine use
Hydromorphone (Dilaudid®)	0.015–0.2 (0.2–0.5 mg every 2–4 hrs PRN)	0.05	3–4	50–70	Commonly used when morphine produces too many undesirable systemic side effects No histamine release
Fentanyl (Sublimaze®)	0.001 (25–50 mcg every 5–15 min in monitored setting)	N/A	0.5–1		Very effective for short painful procedures Vagotonic and can cause bradycardia Minimal hemodynamic alterations Chest wall rigidity/glottis closure Transmucosal dose 10–15 mcg/kg Transdermal patch available for chronic pain
Codeine	N/A	1.2 (15–60 mg every 4–6 hrs PRN)	3–4	40–70	PO only “Prodrug” must be converted by CYP2D6 to morphine to produce analgesia (ultra-rapid metabolizers can produce excessive amounts of morphine, slow metabolizers no analgesia) Often combined with acetaminophen No longer recommended Contraindicated (“black box warning”) in pediatric tonsillectomy patients
Hydrocodone (Vicodin®, Lortab®)	N/A	0.1 (15–60 mg every 4–6 hrs PRN)	3–4	60–80	PO only (liquid and tablet) Only available in combination with acetaminophen DEA class 2 drug
Oxycodone (Tylox®, Percocet®, Oxycontin®)	N/A	0.1 (5–10 mg every 4–6 hrs PRN)	3–4	60–80	PO only Often prescribed with acetaminophen but available as a single agent Liquid formulation 1 mg/mL and 20 mg/mL (potential for catastrophe with wrong formulation) Sustained release tablet available, which cannot be crushed or chewed (Oxycontin®) High abuse potential in sustained release formulation

Table 9.6 PCA dosing guidelines

Drug	Continuous basal infusion (mg/hr)	Demand dose (mg)	Lockout interval minutes (range)	Number of demand doses/hr (range)	4-hour limit (mcg/kg)
Morphine (standard 1 mg/mL)	0.5–1 Rare in adults	1	8 (6–15)	5 (1–10)	250
Fentanyl	0.025–0.05 Rare in adults	0.025	15 (6–15)	4 (1–10)	5
Hydromorphone (standard 0.2 mg/mL)	0.2 Rare in adults	0.2	8 (6–15)	5 (1–10)	50

patients have a higher incidence of OSA secondary to increased soft tissue in and around the pharynx and larynx. This leads to upper airway obstruction and the propensity for disordered breathing during sleep. OSA is estimated to affect 9–24% of middle-aged adults.²⁶ Through a variety of mechanisms, opioids may contribute to airway obstruction, apnea, and hypoxemia. Opioids have a dose-dependent effect on genioglossus tone, which can contribute to airway obstruction.²⁷ The sedative effect of opioids may also contribute to airway closure²⁸ while also altering the arousal thresholds that remain critical in postapneic recovery. Furthermore, postoperative lung volumes are reduced in OSA patients causing upward movement of the diaphragm and carina.²⁹ This reduction in airway length is associated with increased propensity for airway obstruction.³⁰ Postoperative sleep-disordered breathing is related to opioid dose, and some patients with OSA may be more sensitive to opioids.^{31,32} While apneic episodes are likely to be witnessed and corrected in the post-anesthesia care unit, these episodes may go unrecognized on the ward where the nurse-to-patient ratio is lower and patients are monitored less closely.²⁰ Postoperative desaturation is fairly common among this population, and cardiorespiratory complications occur with increased frequency.^{33–36} Cutting the opioid dose in half or increasing the dosing interval with prolonged observation may be prudent to avoid adverse effects. Respiratory failure in OSA patients is transient and ventilatory support is typically needed for 24 hours postoperatively.³⁴ Early utilization of positive airway pressure therapy in the postoperative period is associated with a significant reduction in the incidence of respiratory failure, intubation, and intensive care utilization.^{37–40} Recommendations for postoperative care in this group of patients includes the use of continuous pulse oximetry, opioid restriction, increased length of PACU observation, and early postoperative positive airway pressure therapy.⁴¹

The aging surgical population necessitates an understanding of the effect of opioid administration in these patients. The pharmacokinetics and pharmacodynamics of all medications including opioids may change significantly in the elderly patient. Changing circulating plasma volume and changes in body weight composition may lead to a variable effect. Adverse effects that may be tolerated in younger patients may have more profound effects in the elderly. The addition of opioid side effects may increase the likelihood of falls in the elderly, which can lead to multiple complications with a higher degree of morbidity and mortality. Additional opioid

side effects may contribute to increased all-cause mortality. Furthermore, the elderly are at risk of long-lasting cognitive dysfunction postoperatively from anesthesia independent of postoperative opioid dosing with 17% of patients experiencing dysfunction at 3 months.⁴² Opioid dosing has not been found to have a direct link to cognitive dysfunction postoperatively. Side effects in conjunction with anesthesia increase the risk for cognitive complications. Adjuvant anesthetics play a key role and have been used with much success in reducing opioid administration by 15–55% in the first 24 hours postoperatively. Adjunctive medications such as acetaminophen, NSAIDs, and α -2 agonists may be a mainstay in therapy for the elderly population, lending to adequate anesthesia and limited exposure to opioids.⁴²

It is not uncommon that patients who present for surgery are taking opioids for various reasons. It is important to determine the drug, dose, frequency, and duration in developing a postoperative pain regimen in such patients. Patients who have been taking opioids for a period in excess of 6 months are considered chronic opioid users and are likely to have a tolerance to analgesia and some side effects.²⁰ Additional acute dosing above baseline chronic dosing must be considered while exercising caution because of dose-dependent side effects. Furthermore, patients who have chronic pain and use chronic opioids have more postoperative pain and resolve pain more slowly than opioid-naïve patients.⁴³ Chronic nonmalignant pain is a complicated pathology that may be managed best by consultation with a pain specialist.

Some chronic opioid users adhere to special regimens or drugs including methadone or suboxone. Methadone is used as a long-acting opioid, as well as a drug to facilitate weaning from opioids.⁴⁴ Larger doses may be used for withdrawal prevention. It is essential to determine methadone indications, and communication with the prescribing physician to delineate the analgesic plan for the patient postoperatively.²⁰

Buprenorphine is a unique opioid that tightly binds the opioid receptor, but elicits low activity.⁴⁵ This agent can also be used for chronic pain and opioid addiction. Similar to methadone, discussion with the prescribing physician is essential to allow tapering if indicated. Discussion with the anesthesiologist is also imperative as standard opioid regimens may not be effective immediately postoperatively. Close monitoring is necessary as discontinuation of buprenorphine can lead to increased sensitivity to opioids and the concurrent adverse effects.²⁰

Table 9.7 Summary of adverse effect reduction strategies for opioids in special situations

Description	Risk modification
IV PCA	Opioid reduction strategies: intraoperative and postoperative strategies including adjuvant medications (acetaminophen, ketamine, magnesium, NSAIDs, α 2-agonists, gabapentinoids, and liposomal bupivacaine) and techniques (surgical technique modification and regional and neuraxial anesthesia) Limit/avoid other sedatives
Oral opioids	Limit postoperative prescription and close follow-up Limit/avoid other sedatives Patient education on adverse effects, warning signs Adjuvant medications (acetaminophen, α 2-agonists, gabapentinoids, NSAIDs, and liposomal bupivacaine)
Obesity, OSA	Preoperative screening for OSA Preoperative consideration for polysomnography Opioid reduction strategies: intraoperative and postoperative strategies including adjuvant medications (acetaminophen, ketamine, magnesium, NSAIDs, α 2-agonists, gabapentinoids, and liposomal bupivacaine) and techniques (surgical technique modification and regional and neuraxial anesthesia) Avoid other sedatives (anxiolytics and sleep aids) Consider extended monitoring, although controversial Early postoperative positive airway pressure therapy if significant desaturation occurs Advise sitting or head up reclining posture when sleeping postoperatively
Elderly patients	Opioid reduction strategies: intraoperative and postoperative strategies including adjuvant medications (acetaminophen, ketamine, magnesium, NSAIDs, α 2-agonists, gabapentinoids, and liposomal bupivacaine) and techniques (surgical technique modification and regional and neuraxial anesthesia) Adjuvant analgesia (local, regional, or neuraxial anesthesia, modified surgical technique, and non-sedative analgesics) Avoid other sedatives
Opioid tolerant	Continue chronic opioids High-dose opioid taper Opioid reduction strategies: intraoperative and postoperative strategies including adjuvant medications (acetaminophen, ketamine, magnesium, NSAIDs, α 2-agonists, gabapentinoids, and liposomal bupivacaine) and techniques (surgical technique modification and regional and neuraxial anesthesia) Patient education and establish expectations

IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; OSA, obstructive sleep apnea.

From Momoh AO, Hilliard PE, Chung KC. Regional and neuraxial analgesia for plastic surgery: surgeon's and anesthesiologist's perspectives. *Plast Reconstr Surg*. 2014;134(4 Suppl 2):58S–68S.

NMDA receptor antagonists and gabapentinoids

Ketamine

Ketamine works as a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. The NMDA receptor is activated with sustained and intense pain stimuli, and has been implicated in both immediate hyperalgesia and long-term changes in pain perception that may lead to chronic postsurgical pain (CPSP).^{46,47} Ketamine has also been shown to downregulate proinflammatory pathways, which may be the mechanisms responsible for antihyperalgesia effects.^{47,48}

Ketamine has a half-life of 180 minutes and is metabolized in the liver, and its unique characteristics include the preservation of respiratory drive and hemodynamic stability.^{47,49} The favorable profile of ketamine as an anesthetic agent includes continuous spontaneous breathing as it has minimal respiratory depressant effects and preserves upper airway muscle, pharyngeal, and laryngeal tone. Further favorable characteristics include a mild sympathomimetic effect that results from catecholamine release, and an inhibition of noradrenaline reuptake leading to an increase in heart rate, stroke volume,

and mean arterial pressures.^{46,50} This profile is favorable in hemodynamically unstable patients.

Recent data have demonstrated that ketamine improves analgesia and reduces opioid requirements in the perioperative setting.^{51–54} Furthermore, evidence supports the intraoperative use of ketamine in patients with chronic pain and those on chronic high-dose opioids. Reports demonstrate reduced postoperative pain, as well as reduced opioid consumption.⁵⁵ The use of ketamine has also been associated with a significant reduction of opioid-related side effects including postoperative nausea and vomiting (PONV).^{51,52} Dose-dependent neuropsychiatric effects, including dysphoria, hallucinations, vivid, unpleasant dreams, and catatonia or psychoses are potential side effects of ketamine rendering it unfavorable as a sole anesthetic agent. However, subanesthetic doses have a considerably lower incidence of these adverse effects and seem to be well tolerated.⁴⁹

There is a lack of data with regard to the use of ketamine in plastic surgery patients; however, many conclusions can be extrapolated from the literature and other patient populations. Low-dose ketamine as an adjunct is most beneficial in surgeries where postoperative pain is expected to be high.⁵¹ The sympathomimetic effects in conjunction with decreased intraoperative and postoperative opioid requirements may help to preserve hemodynamic stability and decrease the

need for perioperative vasopressor use. Decreasing the need for perioperative vasopressor use would be ideal for flap perfusion.⁴⁹

At subanesthetic doses (0.5 mg/kg bolus or 0.1 mg/kg/h), ketamine improves analgesia and reduces opioid requirements. This effect seems most significant in surgeries that are expected to be painful and have a moderate and high degree of pain. Furthermore, the sympathomimetic effects may be beneficial in maintaining hemodynamic stability. Psychiatric side effects such as dysphoria and hallucinations seem to be far less common than with anesthetic doses of ketamine (1–5 mg/kg), and are reported by multiple authors to be well tolerated.⁴⁹

Gabapentinoids

Gabapentin and pregabalin are alkylated analogs of gamma-aminobutyric acid (GABA). Gabapentin was originally developed as an anticonvulsant.⁴⁶ Neither of these agents exert their clinical effects by way of the GABA-A or GABA-B receptors. Instead, they seem to bind voltage-gated calcium channels of cortical and dorsal horn neurons, attenuating the release of the neuropeptides glutamate, norepinephrine, and substance P.^{46,50} Furthermore, gabapentin may activate descending inhibitory noradrenergic pathways that regulate the neurotransmission of pain signals in the dorsal horn.^{50,56}

Gabapentin has been used successfully in several neuropathic pain states including complex regional pain syndrome, multiple sclerosis, and postherpetic neuralgia.^{57–61} Pregabalin has also been found to be useful in diabetic neuropathy.⁶² Both agents are only available as oral preparations and differ in bioavailability.

Several studies have concluded that both gabapentin and pregabalin reduce both postoperative pain and opioid use postoperatively. Overall the gabapentinoids are well tolerated with the most common transient adverse effects of somnolence, dizziness, headaches, balance problems, peripheral edema, sweating, dry mouth, and nausea and vomiting.^{46,50,63,64} There remains some debate about the timing and dose of administration. Higher preoperative doses seem to provide better analgesia although sedation may be seen. The optimal duration of postoperative administration remains to be determined. The overall risk–benefit ratio is likely to favor their use in procedures that are expected to be painful or that might cause acute neuropathic pain.⁴⁹

Local anesthetics

Major improvements in local anesthetic injection and application techniques have allowed surgeons more flexibility. Minimizing pain with injection has led to an increase in convenience while maintaining patient safety and comfort. The wide-awake approach without sedation has proven to be effective in hand surgery,⁶⁵ cosmetic surgery,⁶⁶ facial skin cancer reconstruction,⁶⁷ and adult cleft lip repair⁶⁸ among others.

Minimizing pain with injection of local anesthesia (Box 9.1)

Blunt-tipped cannulae have been shown to be effective for the infiltration of HA fillers in sensitive areas with minimal pain.⁶⁹

BOX 9.1 Tips for minimizing pain with injection of local anesthesia

- Create skin perforation with a 27-gauge needle
- Switch to a 30-gauge blunt-tipped cannula for injection when possible
- To promote painless injection of local anesthesia with sharp needles:
 1. Buffer lidocaine and epinephrine with 8.4% sodium bicarbonate
 2. Warm the local anesthetic
 3. Distract the patient or area of injection with pressure or soft pinch near the point of injection
 4. Use smaller 27- or 30-gauge needles
 5. Stabilize the syringe with both hands to avoid movement of the needle
 6. Inject 0.5 cc perpendicular to the dermis, and subdermally, followed by a pause until the patient reports no further needle pain
 7. Inject an additional 2 cc before moving the needle followed by moving and injecting in an anterograde fashion slowly with 1 cm of local anesthetic palpable or visible ahead of the needle
 8. Always reinsert needles within 1 cm of blanched areas
 9. Have patients frequently provide feedback and pain scores during the injection process

Following skin perforation with a 27-gauge needle, a fine blunt-tipped 30-gauge cannula is introduced. This method allows for the painless passing of cannulae beneath the skin for injection of large areas with local anesthesia with little to no pain. Furthermore, far less ecchymosis results without the use of a sharp needle tip.⁷⁰

Injecting local anesthesia with traditional sharp needles in an almost painless manner is readily achievable.^{68,71} When injecting with sharp needles, the pain of injection can be mitigated by (1) buffering lidocaine and epinephrine with 8.4% sodium bicarbonate; (2) warming the local anesthetic; (3) distracting the patient or the area of injection (pinch or pressure near the injection point); (4) using smaller 27- or 30-gauge needles; (5) stabilizing the syringe with both hands to avoid movement of the needle; (6) injecting 0.5 cc perpendicularly subdermally followed by a pause until the patient reports no further needle pain; (7) injecting an additional 2 cc before moving the needle followed by moving and injecting in an anterograde fashion very slowly with 1 cm of local anesthetic palpable or visible ahead of the needle; (8) reinserting needles within 1 cm of blanched areas; and (9) having patients provide feedback and scores by relaying pain during the injection process.⁶⁷

Liposomal delivery of local anesthetics

Liposomal bupivacaine offers long-lasting local anesthesia by means of sustained, gradual delivery. With exposure over time, the vesicular network opens successively thereby releasing the local anesthetic content. With liposomal bupivacaine in Exparel (Pacira Pharmaceuticals, Inc, San Diego, CA), 3% of the bupivacaine is initially free at the time of injection for an immediate effect as with traditional bupivacaine, while the

remainder is contained within the vesicles for gradual delivery.⁷⁰ While there is evidence purporting a potentially positive early experience with liposomal bupivacaine for wound infiltration, further evidence for its use in plastic surgery is needed. In particular, it is not FDA-approved for epidural or peripheral nerve block administration and these routes of administration are currently being investigated.

Local anesthetic infiltration into operative sites (wound infiltration)

The injection of bupivacaine into TRAM flap donor sites decreases opiate requirements in the 72 hours postoperatively.⁷² In another study, patients who received bupivacaine (0.375%) infused at 4 mL/h used less mean patient-controlled anesthesia narcotic in the immediate 48 hours postoperatively, and transitioned to oral narcotics earlier than control patients. Overall pain satisfaction scores were significantly improved in the continuous infusion group in comparison to the control group.⁷³ Furthermore, ropivacaine injection into cleft palate incision sites demonstrated significantly improved postoperative pain scores at all observational periods in comparison to the control groups.⁷⁴

Local anesthetic infiltration via a wound catheter and a pain pump have shown favorable outcomes in other specialties.⁷⁵ With respect to plastic surgery, there is evidence to show that bupivacaine wound catheters reduce narcotic use, nausea and vomiting, and increase overall pain satisfaction scores.^{73,76} Further studies are necessary to elucidate the advantages of routine catheter usage in plastic surgery. Maximum dosing recommendations for different anesthetic techniques are outlined in [Table 9.8](#).

Tumescent analgesia in plastic surgery

Tumescent analgesia (TA) delivers a very dilute anesthetic subcutaneously in a large volume of fluid. This form of local anesthesia is used most commonly in liposuction, but may be used in a variety of procedures to reduce intraoperative and postoperative pain, and decrease the need for additional anesthetics and narcotics. The added benefit of dilute epinephrine causes vasoconstriction and significantly limits blood loss.

TA was popularized in the 1990s by Klein for use during liposuction.⁷⁷ Currently, TA can be used alone or in conjunction with other forms of anesthesia. When used in conjunction with other modalities, TA offers several of the ascribed advantages of multimodal anesthesia.

Tumescent analgesia has been reported in a wide array of surgical procedures including:

- Liposuction
- Subcutaneous mass excision and scar revisions
- Excisional body contouring (abdominoplasty, body lifts, brachioplasty, thigh lifts)
- Breast augmentation, reduction, mastopexy, gynecomastia, and capsular contracture revision
- Mastectomy
- Burn excision and skin grafting
- Skin procedures (dermabrasion and laser resurfacing)
- Face and neck lifts
- Hair grafting
- Lower extremity varicose vein stripping and endovascular ablation
- Lymph node dissections

Table 9.8 Maximum local anesthetic dosing guidelines

Amide drug (concentration range)* and technique concentration range	Spinal	Caudal/lumbar epidural	Peripheral	Subcutaneous
Lidocaine (0.5%–2.0%) (0.5–1.0% infiltration) (1–2% peripheral, epidural, subcutaneous) (5% spinal)	1–2.5	5–7 [§]	5–7 [§]	5–7 [§]
Bupivacaine (0.0625–0.5%) (0.125–0.5% infiltration) (0.25–0.5% peripheral, epidural, subcutaneous)	0.3–0.5	2–3 [§]	2–3 [§]	2–3 [§]
Ropivacaine (0.0625–0.5%) (0.125–0.5% infiltration) (0.2–0.5% peripheral, epidural, subcutaneous)	0.3–0.5	2–3 [§]	2–3 [§]	2–3 [§]
Prilocaine (0.5–1% infiltration) (1–1.5% peripheral) (2–3% epidural)	NR	5–7 ^{§#}	5–7 ^{§#}	5–7 ^{§#}
Intra-arterial or intravenous injection of these doses may result in systemic toxicity or death. *Concentrations are displayed in mg percent. Example, a 1% solution contains 10 mg/mL, a 2% solution contains 20 mg/mL. §The higher dose is recommended only with the coadministration of epinephrine 1:200,000. Maximum epinephrine dose for adults under general anesthesia with volatile agents is 2–3 mcg/kg. #Total adult dose should not exceed 600 mg.				

- Thyroidectomy
- Hernia repair

Fluid composition

Several TA fluid formulas have been described⁷⁷⁻⁷⁹ and are based on either 1000 mL of 0.9% saline or Lactated Ringer's solution.⁸⁰ Lidocaine is the most frequently used local anesthetic in tumescent fluid, however various local anesthetics have been used. A combination of lidocaine and bupivacaine has been described in abdominoplasty combined with liposuction without any complications.⁸¹ In patients with liver dysfunction, care should be taken with dosing as the amide agents (lidocaine, bupivacaine, ropivacaine) are metabolized by the liver. Furthermore, while lidocaine and bupivacaine can safely be used in combination, there is little guidance with respect to the upper limits of dosing when used in combination.⁸⁰

The reported dose limitation for lidocaine with epinephrine is 7 mg/kg; however, doses of 35 mg/kg are frequently used during liposuction,⁷⁷ and up to 55 mg/kg have been reported without complications.⁸² Peak lidocaine blood levels occur 10–14 hours following infiltration.⁸³ In highly vascularized areas, such as above the clavicle, plasma lidocaine levels peak at approximately 6 hours after injection.⁸⁴ Due to peak plasma concentrations occurring several hours following injection, patients may experience toxicity well after the procedure has been completed and following discharge.

Epinephrine in tumescent analgesia

The maximal hemostatic effects of epinephrine occur 25 minutes after administration rather than the commonly held belief that this occurs at 7–10 minutes.⁸⁵ However, only a minimal improvement in the hemostatic effect is achieved after 15 minutes. Epinephrine has a 2–3 minute half-life, and therefore there are no clear dosing guidelines when used in TA. An upper limit of 10 mcg/kg has been suggested but this depends on cofactors like the co-administration of volatile anesthetic agents. Arrhythmias can develop in adults under general anesthesia with isoflurane, sevoflurane or desflurane with as little as 2–3 mcg/kg. Pediatric patients appear to tolerate 10 mcg/kg under volatile anesthesia without arrhythmias. Epinephrine should be avoided in patients with pheochromocytoma, hyperthyroidism, severe hypertension, cardiac disease, or peripheral vascular disease.⁸⁶

Complications of tumescent anesthesia

Though complications are rare, one must be aware of possible complications particularly in high volume tumescent infiltration. Lidocaine is commonly used in doses of 35–55 mg/kg and this is considered safe in TA. Cardiac monitoring is suggested with doses over 35 mg/kg as lidocaine toxicity can cause cardiac and neurologic complications. In cases of high volume infiltration, extended monitoring is suggested due to peak plasma levels occurring 10–14 hours after administration. Signs and symptoms of lidocaine toxicity include restlessness, drowsiness, light-headedness, metallic taste in the mouth, tinnitus, slurred speech, and peri-oral numbness and tingling. At higher plasma levels, shivering, muscle twitching, tremors, convulsions, central nervous system

depression, coma, respiratory depression, and cardiac arrest may occur.^{80,86}

In the event of local anesthetic toxicity, the following steps must be taken:

1. Stop infusion of fluids with local anesthetic
2. Assure airway management and oxygenation
3. Call for help
4. Prepare for seizure suppression with benzodiazepines
5. Manage cardiac arrhythmias as per ACLS protocol but do not use lidocaine
6. Administer 20% Intralipid 1.5 mL/kg (may need to repeat up to 10 mL/kg) then infuse 0.25 mL/kg/h if cardiac effects persist
7. Isolated neurologic events (seizures) can be treated with benzodiazepines (midazolam, diazepam, or lorazepam) or propofol. Propofol should NOT be used as a lipid substitute for cardiac arrest.

High tumescent fluid injection volumes may lead to intravascular fluid overload with cardiac and pulmonary consequences. With high infusion volumes, administration of other fluids must be titrated. In patients with cardiac, pulmonary, or renal compromise who are at higher risk for fluid overload, the volume of TA administration must be limited.⁸⁰

In large volume liposuction, mild hyponatremia and hypokalemia may occur. This is rarely a clinical concern, but nevertheless, one must be aware of this potential problem in large volume liposuction.⁸⁷ Furthermore, large volumes of room temperature tumescent fluid may lower body temperature. Therefore, in cases prone to hypothermia, such as large volume, and large surface area, tumescent fluid should be warmed to 37°C, in addition to other warming measures to avoid hypothermia.⁸⁰

Regional and neuraxial analgesia in plastic surgery

Regional analgesic modalities deliver local anesthetics to groups of peripheral nerves outside the central nervous system, thereby blocking sensation to specific dermatomes. Neuraxial techniques deliver local anesthetic and analgesic agents directly or indirectly to the spinal cord or neuraxis. The benefits of regional and neuraxial techniques parallel those of multimodal anesthesia and include improved pain control, decreased narcotic use, and narcotic-associated side effects, shorter hospital stays, and better patient-reported outcomes.⁸⁸

Paravertebral block

The paravertebral block (PVB) involves the injection of a local anesthetic into the paravertebral space. The thoracic paravertebral space is triangular in shape and is bordered anteriorly by the parietal pleura, medially by the vertebral column, and posteriorly by the superior costotransverse ligament. The nerve root divides into dorsal and ventral rami as it exits the neuroforamen. Ventral rami become the intercostal nerves that provide sensation to the abdomen and chest wall. This targets the nerve root as it emerges from the neuraxis (Fig. 9.1), thereby providing ipsilateral analgesia in the specific

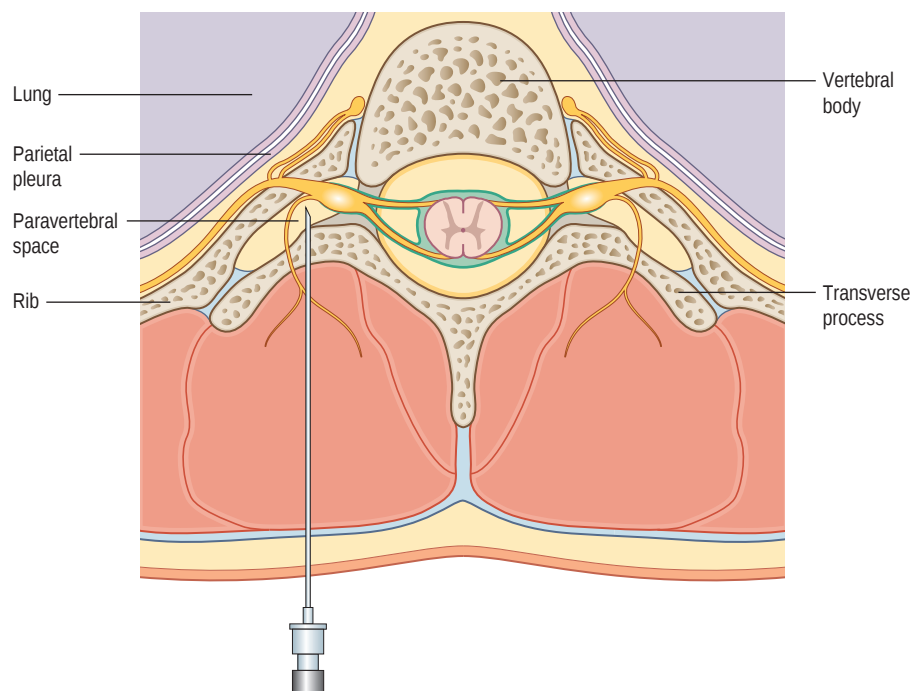


Fig. 9.1 Paravertebral anatomy. (Adapted from Momoh AO, Hilliard PE, Chung KC. *Regional and neuraxial analgesia for plastic surgery: surgeon's and anesthesiologist's perspectives*. *Plast Reconstr Surg*. 2014;134(4 Suppl 2):58S–68S.)

dermatomal segments.⁸⁸ In contrast to neuraxial analgesic techniques, the central nervous system is usually avoided along with the associated complications such as hypotension, urinary retention and bradycardia.

Long-lasting analgesia can be achieved by inserting a catheter into the paravertebral space to provide continuous infusion of local anesthetic in the early postoperative period.^{89,90} Depending on the location of the block, this technique can be used in breast, thoracic, and abdominal procedures. Indications and contraindications for paravertebral and neuraxial blocks are outlined in [Table 9.9](#). While PVBs facilitate outpatient surgical management and early discharge by providing long-lasting analgesia with few side effects, this technique poses a risk for pneumothorax due to the proximity of the lung to the paravertebral space. Although this risk is less than 1%, this potential complication is likely a major

reason for the limited use of PVBs in outpatient plastic surgery procedures. Use of ultrasound guidance helps avoid this complication. Additional complications include epidural spread, hypotension, bradycardia, and intravascular injections may cause toxicity.⁸⁸

Transversus abdominis plane block

The transversus abdominis plane (TAP) block places a long-acting local anesthetic in the fascial plane between the transversus abdominis and the internal oblique ([Fig. 9.2](#)). This technique blunts the afferent sensory component of the terminal branches of intercostal nerves resulting in analgesia of the abdominal wall. In the traditional TAP block, the tenth thoracic (T10) through first lumbar (L1) terminal branches are the nerves typically targeted. The fascial plane between the

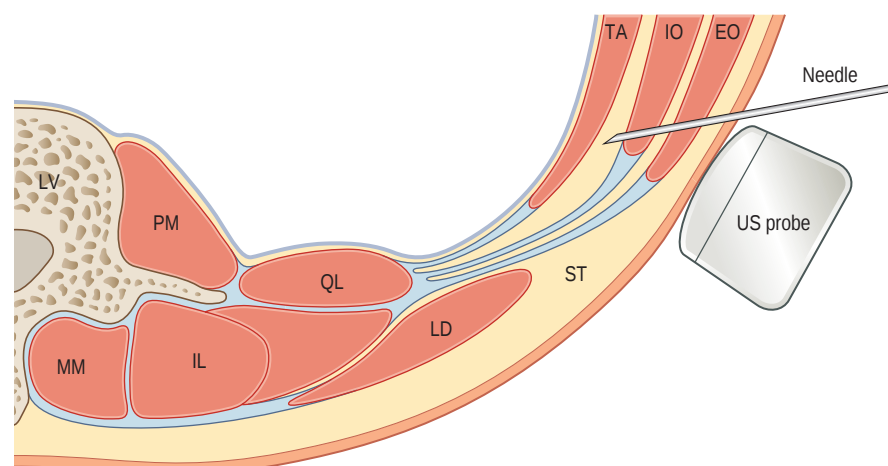


Fig. 9.2 Transversus abdominis plane block anatomy. EO, external oblique; IL, longissimus iliocostalis; IO, internal oblique; LD, latissimus dorsi; LV, lumbar vertebra; MM, multifidus muscle; PM, psoas major; QL, quadratus lumborum; ST, subcutaneous tissue; TA, transversus abdominis muscle. (Adapted from Momoh AO, Hilliard PE, Chung KC. *Regional and neuraxial analgesia for plastic surgery: surgeon's and anesthesiologist's perspectives*. *Plast Reconstr Surg*. 2014;134(4 Suppl 2):58S–68S.)

Table 9.9 Indications and contraindications for regional and neuraxial techniques

Technique	Performed by	Indications	Contraindications
Paravertebral block	Anesthesiologist	Thoracic and abdominal surgical procedures Use as primary anesthetic or as adjunct to primary anesthetic Inpatient and ambulatory surgery procedures Rescue analgesia after failure of oral or parenteral analgesia Early postoperative mobilization desired	Patient refusal Coagulopathy or bleeding diathesis Localized infection at injection site Allergy to local anesthetics Prophylactic anticoagulation therapy* Inability to communicate with patient*
Transversus abdominis block	Anesthesiologist or surgeon	Lower abdominal surgical procedures Adjunct to primary anesthetic Inpatient and ambulatory procedures Early postoperative mobilization desired	Patient refusal Localized infection at injection site Allergy to local anesthetics
Epidural	Anesthesiologist	Thoracic, abdominal, and lower extremity surgical procedures Use as primary anesthetic or as adjunct to primary anesthetic Indwelling catheter for postoperative analgesia limited to inpatient procedures only	Patient refusal Coagulopathy or bleeding diathesis Localized infection at injection site Systemic infection Allergy to local anesthetics Elevated intracranial pressure Severe hypovolemia Severe aortic or mitral stenosis Prior back surgery at injection site* Prophylactic anticoagulation therapy* Inability to communicate with patient*

*Relative contraindication

From Momoh AO, Hilliard PE, Chung KC. Regional and neuraxial analgesia for plastic surgery: surgeon's and anesthesiologist's perspectives. *Plast Reconstr Surg.* 2014;134(4 Suppl 2):58S–68S.

transversus abdominis and internal oblique is a relatively avascular plane and this may account for the slow drug clearance and subsequent prolonged duration of analgesia.^{91,92} The TAP block can be performed intraoperatively by anesthesiologists or surgeons with ultrasound guidance percutaneously or directly through exposed fascia (Fig. 9.3). The TAP block is typically used in combination with other anesthetic modalities as its primary analgesic effects are within the abdominal wall and may not address visceral pain associated with intra-abdominal procedures.⁸⁸

The ultrasound probe is placed within the lumbar triangle of Petit, the boundaries of which are the costal margin superiorly, the iliac crest inferiorly, the external oblique anteriorly, and the latissimus dorsi posteriorly. Local anesthetic is then infiltrated in the fascial plane between the internal oblique and transversus abdominis. Catheters may be placed for continuous or intermittent infusion. A subcostal approach to the TAP block is also possible and provides analgesia to the supraumbilical abdomen (T7–T9). The subcostal TAP block is unlikely to be used alone as most abdominal procedures in plastic surgery also involve the lower abdomen.⁸⁸

Though complications are rare with the TAP block, they include hematoma and intraperitoneal injection with injury to intra-abdominal organs.^{93–95}

Neuraxial analgesia

Spinal and epidural anesthesia

Spinal anesthesia is a neuraxial blockade of spinal nerve roots as they travel through the subarachnoid space. This type of

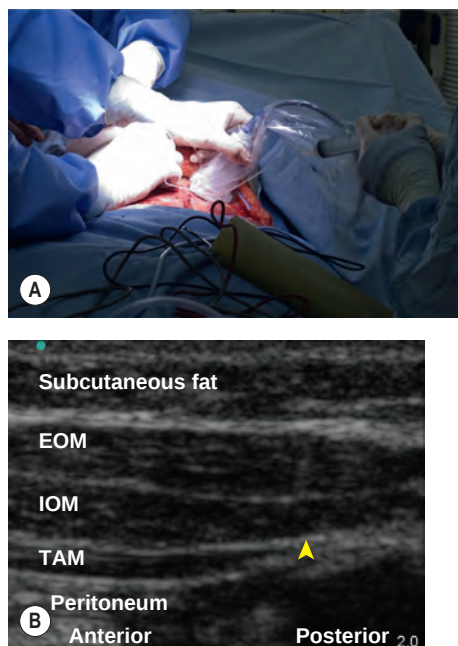


Fig. 9.3 (A) Intraoperative, ultrasound-guided delivery of TAP block. Note concurrent inset of flap in background. (B) Ultrasound scan of transversus abdominis plane (TAP) block. EOM, external oblique muscle; IOM, internal oblique muscle; TAM, transversus abdominis muscle. (A, from Whebl GAC, Tan EKH. Transversus abdominis plane block in autologous breast reconstruction: a UK hospital experience. *J Plast Reconstr Aesth Surg.* 2013;66(12):1665–1670. © British Association of Plastic, Reconstructive and Aesthetic Surgeons 2013. B, from Ross AK, Bryskin RB. Regional anesthesia. In: Davis PJ, Cladis FP, Motoyama EK (eds). *Smith's Anesthesia for Infants and Children.* 2011;452–510. © Mosby 2011.)

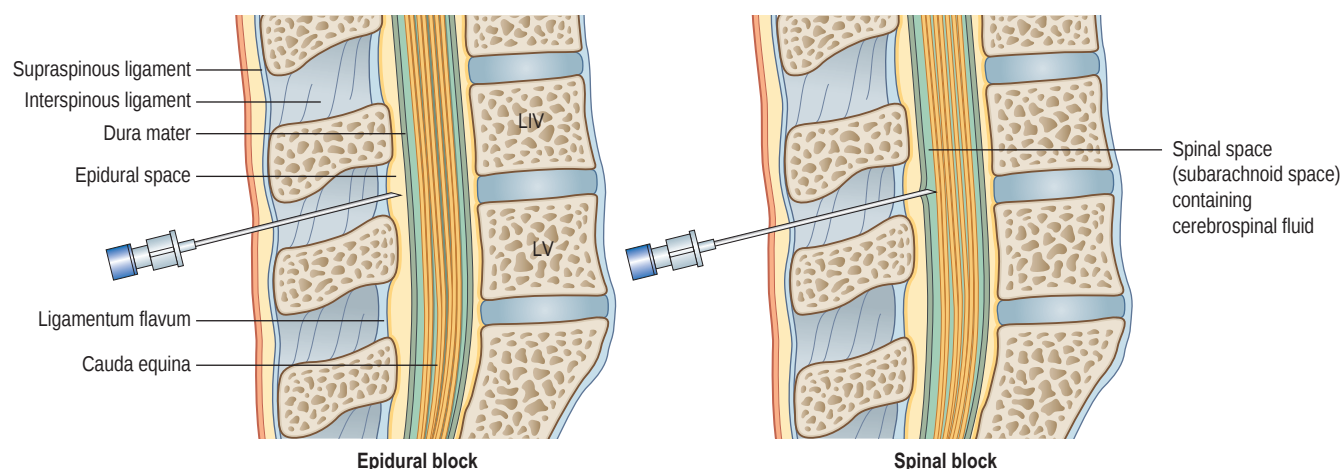


Fig. 9.4 Needle placement for medication delivery in spinal and epidural anesthesia. (Adapted from Momoh AO, Hilliard PE, Chung KC. *Regional and neuraxial analgesia for plastic surgery: surgeon's and anesthesiologist's perspectives*. *Plast Reconstr Surg*. 2014;134(4 Suppl 2):58S–68S.)

block is also frequently referred to as a subarachnoid block, or intrathecal injection. This technique provides rapid and deep anesthesia below the level of the block, and is generally confined to shorter procedures of the lower extremities or pelvis, therefore limiting its utility in a large portion of plastic surgery procedures.

Epidural anesthesia blocks the spinal nerve roots outside of the subarachnoid space (Fig. 9.4). It has a wide range of applications including operative anesthesia, obstetric and postoperative analgesia, and chronic pain management. The epidural technique is advantageous because it allows a catheter to be placed in the epidural space anywhere along the neuraxis to provide continual analgesia via infusion. Thoracic epidurals may spare motor nerves to the lower extremities as well as micturition pathways, thereby allowing for early ambulation and the avoidance of prolonged urinary catheter use. An epidural may be used as the primary anesthetic for surgery, but typically this requires high doses of local anesthetic and is often combined with other modalities.⁸⁸ The epidural is an excellent form of analgesia for surgery involving the lower extremities, particularly reconstruction with microvascular work. The sympathectomy may provide an advantage by enhancing blood flow to the extremity.

Lumbar neuraxial procedures are performed with the patient in the seated position (Fig. 9.5). Full neck and back flexion overcomes lumbar lordosis by widening the gap between adjacent lumbar spinous processes. This opens the interlaminar space and facilitates access to the neuraxis. The L3/L4, L4/L5, or L5/S1 interspaces are frequently chosen for analgesia of the pelvis and lower extremities. It is prudent to place a Foley catheter and implement fall precautions when epidurals are used in the postoperative period.⁸⁸

Complications of the epidural blocks are typically related to technique or physiologic effects of the neuraxial injection. Complications related to technique include spinal headaches, transient paresthesias, peripheral neuropathy, epidural abscesses, and epidural hematomas. Physiologic complications include cardiovascular, respiratory, thermoregulatory, and urogenital sequelae.

Cardiovascular effects are not uncommon and typically include hypotension with an incidence as high as 33%.⁹⁶

Cardiovascular sequelae are primarily due to efferent sympathetic blockade leading to an uncompensated decrease in systemic vascular resistance. A decrease in preload in conjunction with an unopposed vagal influence leads to a decreased heart rate and cardiac output.⁹⁷ Hypotension and bradycardia are usually mild and readily respond to treatment.⁸⁸

Respiratory complications typically occur as a result of blockade of the intercostal and abdominal muscles needed for forceful exhalation. Inhalation remains unaffected as the diaphragmatic innervation is spared. While accessory muscles are not essential for expiration in healthy patients, those with pulmonary disease such as asthma or COPD may be prone to complications. Therefore, careful patient selection is crucial, as is the preparedness to manage these potential complications.⁸⁸

The majority of regional and neuraxial techniques are better established in other surgical fields including general surgery, urologic surgery, and gynecologic surgery. However, applications in plastic surgery are increasing. These techniques are best implemented in collaboration with anesthesiologists.⁸⁸



Fig. 9.5 Placement of a thoracic epidural block for postoperative pain control. (From Barrington MJ, Scott DA. *Do we need to justify epidural analgesia beyond pain relief?* 2008;372:514–516. © Lancet 2008.)

Summary

One of the most common concerns reported by patients prior to surgery is the presence of postoperative pain.² Evidence reveals that adequate postoperative analgesia is only achieved in a minority of patients.⁹⁸ Furthermore, reports in the United States reveal that 86% of adult surgical patients experienced pain after surgery, of which 75% had moderate-to-severe pain in the immediate postoperative period, and 74% experienced similar levels of pain after being discharged home.⁹⁹ These findings reveal that advances in surgical and analgesic techniques have had minimal clinical effect on postoperative pain management.¹⁰⁰

It is well established that unrelieved postoperative pain is linked to adverse physiologic changes that may increase adverse postoperative outcomes including morbidity and mortality.³ Furthermore, limitations in movement secondary to pain can prolong rehabilitation, reduce health-related

quality of life, and delay return to normal daily activities.^{5,100–103} Increased cost of care, prolonged hospital length of stay, readmissions, or unexpected admissions, and patient dissatisfaction are common consequences of these adverse outcomes.^{104–106}

The concept of multimodal analgesia was developed with the understanding that postoperative pain is a complex and multifactorial phenomenon. As such, combinations of analgesics of different classes acting upon various target sites may provide superior pain relief with a lower incidence of adverse effects.^{107–109} The goal of multimodal analgesia is to improve pain relief while reducing opioid requirements and the adverse effects of opioids or any other single agent.

Future considerations include establishing sufficient evidence for multimodal analgesia in plastic surgery while optimizing analgesic regimens. Use of patient-specific and procedure-specific pain management strategies should improve pain control, and perioperative outcomes including rehabilitation and return to activities of daily living.



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Evidence-based medicine and health services research in plastic surgery

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SYNOPSIS

The key take-home messages from this chapter are how to:

- Gather existing evidence on outcomes
- Interpret evidence on outcomes
- Design new studies to add evidence on outcomes
- Identify and analyze existing sources of data to create new evidence on outcomes
- Capture the patients' perspective on outcomes
- Recognize the importance of an essential dimension of evidence: the patients' perspective
- Consider the cost dimension in achieving outcomes
- Understand the challenges and approaches in translating good evidence into daily clinical practice.

Physicians must make complex decisions in situations of uncertainty – often with incomplete, inaccurate, or outdated information. The goal of outcomes research is to improve the information available to make these complex decisions. It is important to understand that measuring outcomes is not just about the final result of our interventions. More importantly, it is a means by which we gather evidence to improve decision-making, the processes of care, and the systems in which we work. Maximizing patient care and surgical outcomes requires continuous efforts to identify information needs and to produce the best evidence to fulfill these needs.

The best evidence – where do we find it?

There are two ways to obtain best evidence for decision-making to improve quality of care (Fig. 10.1). The first is to evaluate existing data and identify those reports that are convincing based on a good study design and clinically meaningful outcomes. When the current evidence is inadequate, the second choice is to produce new credible evidence. This section

will describe a structure for evaluating existing evidence and then introduce methods for producing best evidence.

Evaluating existing literature

Best evidence requires three things: (1) a good study design; (2) an appropriate statistical analysis; and (3) clinically meaningful outcome measures. In a thorough review, Offer and Perks¹ have enumerated the challenges that plastic surgeons face when trying to practice evidence-based medicine. They cite the lack of quality evidence in our literature as a major factor. Even a superficial perusal of our journals makes it clear that they are replete with descriptions of procedures by individual surgeons and the “outcomes” of those procedures in that surgeon's hands. These studies, known as case reports or case series, have limited applicability to other practices, and are not structured, not compared, and not randomized. This is not only weak evidence on which to make medical decisions, but it is not an acceptable way to make such decisions in this era of healthcare reform and pay for performance (P4P).² As shown in Fig. 10.1, the stronger the evidence, the better the care one is able to deliver.

Literature search strategies

Practicing evidence-based medicine involves searching for the best available research, appraising the relevant studies for validity, and then translating the evidence to optimize patient care.³ Many clinical questions remain unanswered because of problems formulating relevant questions, insufficient access to information resources, and a lack of search skills.⁴ Today, there are a variety of strategies and web-based resources that allow searches of the relevant literature to answer many clinical questions. Some examples are provided below.

PubMed

The US National Library of Medicine provides access to more than 16 million citations through PubMed, accessing references from MEDLINE and directly from journals. Information

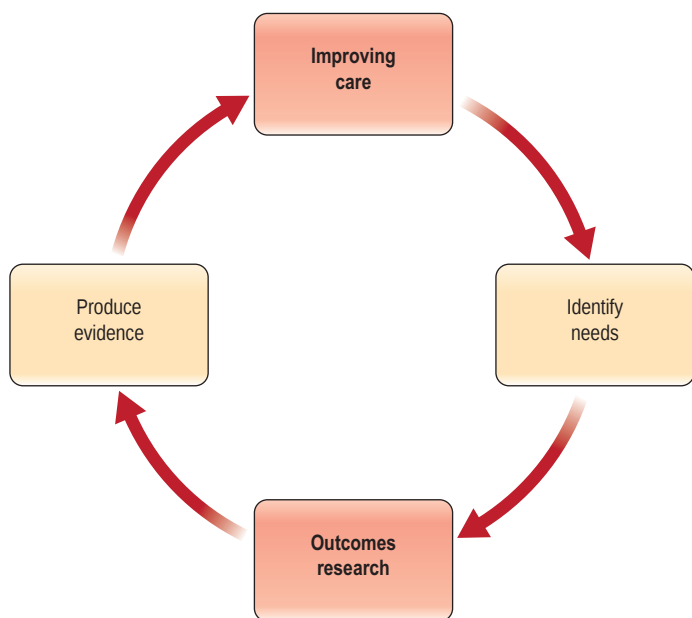


Fig. 10.1 Improved care is linked to better evidence.

from PubMed searches has been shown to improve both patient care and health outcomes significantly.⁴

Clinical Queries

Clinical Queries is a feature of PubMed that can help identify citations with the study design of interest. It is able to link the type of question (e.g., intervention, diagnosis, natural history, and outcome) to a search strategy that specifies the desired study design.⁴

PICO

The critical first step in the pursuit of evidence-based medicine is to ask a well-formulated question. Without sufficient focus and specificity, an otherwise relevant and important clinical question can be mired in irrelevant evidence. When the PICO framework is used with the PubMed Clinical Queries (see above), it has been shown to improve the efficiency of the literature search. The acronym PICO stands for patient problem, intervention, comparison, and outcome, and is a strategy to pose a well-formulated question.⁴ In a literature search for evidence in plastic surgery, for example, a question framed using the PICO approach might be expressed this way: In patients undergoing breast reduction (P), preoperative antibiotic prophylaxis (I) versus no prophylaxis (C), what is the rate of postoperative infections (O)?

Meta-analysis

Conceptually, a meta-analysis is the summation of multiple qualitative studies in order to increase the sample size, thus strengthening the conclusions over that which can be drawn from an individual article. This analysis allows researchers to reach a more reliable conclusion when there are conflicting results from multiple studies.⁵ Ideally, a meta-analysis is conducted using the highest level of evidence, such as randomized controlled clinical trials. Although meta-analysis can also be conducted on cohort studies and even case series, the quality of the evidence and, therefore, the conclusions are weaker.

Meta-analysis has some disadvantages. First, meta-analysis has been criticized for both overly broad inclusion criteria and, conversely, for overly strict inclusion criteria. Either may result in degradation of the results. Inclusion criteria that are overly broad may lead to inclusion of studies of lesser quality or with less reliable results. Very strict inclusion criteria may mean that the studies that are included have limited generalizability. Another disadvantage is that meta-analyses are costly and require a significant time commitment from the research team.

The technique of meta-analysis may have limited applicability in plastic surgery, where there are few randomized trials and the metrics from one study to another may vary considerably. An example of a meta-analysis can be seen in Fig. 10.2.⁶ This figure demonstrates an analysis of randomized trials evaluating the impact of tamoxifen on survival. As the reader can observe, there are multiple studies, with the findings of each plotted on a central axis. The summary analysis, which incorporates data from these studies, appears at the bottom of the vertical axis and suggests a benefit for the use of tamoxifen in early breast cancer. As can be seen, the 95% confidence interval for that summary measure is quite narrow. This implies a better point estimate of the true benefit of tamoxifen. Also note that the quality of the individual study is used to determine its weight in computing the summary score.

More recently, researchers conducted a meta-analysis of randomized controlled trials comparing rates of capsular contracture using either smooth or textured implants. These authors identified seven randomized controlled trials that addressed this issue. Individually four of the seven studies did not find a statistically significant decrease in the rate of contracture with textured implants. However, when the results of the studies were pooled, the meta-analysis suggested that textured implants had lower rates of contracture.⁷ To see further examples of good-quality meta-analyses, the reader is referred to the online Cochrane reviews.⁸

Systematic reviews

Systematic reviews are evaluations of the literature conducted according to clearly stated, scientific research methods that are designed to minimize the risk of bias and the errors associated with traditional literature reviews. The review process includes a comprehensive search based on defined criteria and includes a thorough evaluation of the quality and validity of the studies identified in the search process.⁹

The best-known source for systematic reviews is the Cochrane Database of Systematic Reviews, which contains over 3600 completed reviews.⁸ The Cochrane Group also provides a handbook for systematic reviews of interventions which prescribes seven steps for preparing a review:

1. Structuring the question
2. Identifying possible studies for inclusion
3. Evaluating selected studies
4. Data collection and synthesis
5. Analyzing results
6. Discussing the findings
7. Updating reviews

Systematic reviews are influential tools in supporting evidence-based practice and some consider them to provide stronger evidence than randomized controlled trials. Moreover, they are essential for summarizing existing data, thereby

Review: Tamoxifen for early breast cancer
Comparison: 01 Adjuvant tamoxifen versus control
Outcome: 02 Mortality (death from any cause)

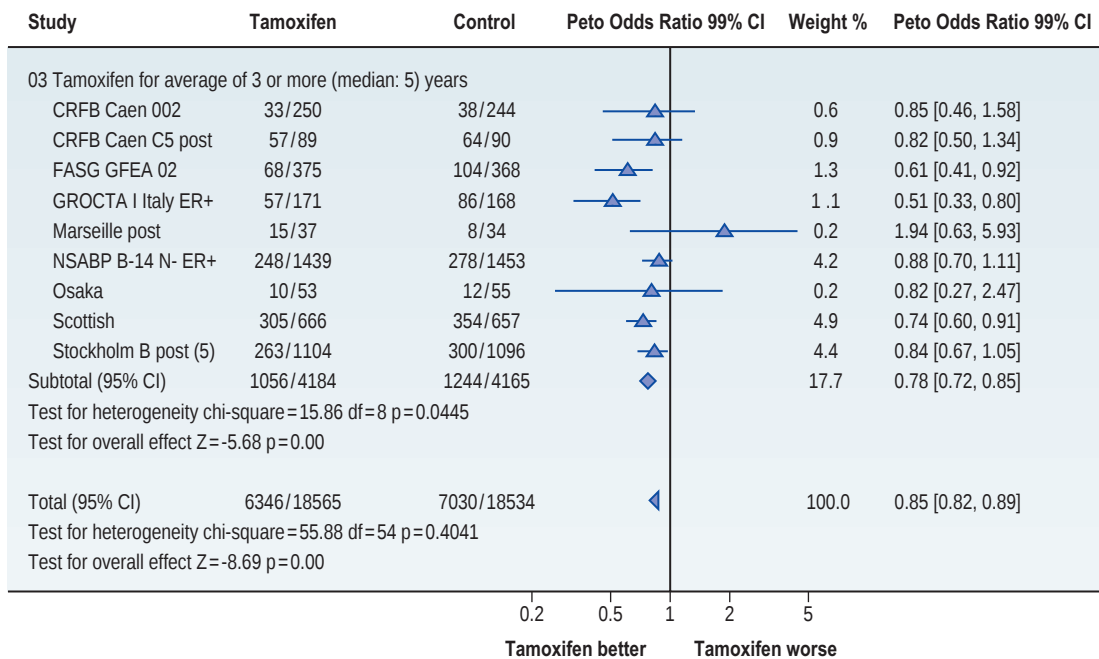


Fig. 10.2 Meta-analysis of randomized controlled trials evaluating the impact of adjuvant tamoxifen on survival risk among women with early breast cancer. (Early Breast Cancer Trialists' Collaborative Group. *Tamoxifen for early breast cancer. Cochrane Database of Systematic Reviews. 2001:4.*) Multiple studies have been included, with the findings of each plotted on the central axis. Data are represented as an odds ratio. (Odds ratio, similar to relative risk, reports the proportion of an occurrence to a nonoccurrence.) The summary analysis, which incorporates data from these studies, appears at the bottom of the vertical axis and suggests a benefit for the use of adjuvant tamoxifen in early breast cancer.

avoiding the wasted effort that would result from unnecessary duplication of previous studies.⁹ To see further examples of good-quality systematic reviews, the reader is referred to the online Cochrane reviews.

Study design and levels of evidence

Broadly, study designs can be divided into experimental and observational studies. Experimental studies, which include randomized controlled clinical trials, patient preference trials, and large, multicenter trials, test a hypothesis by examining the impact of an intervention on the outcome. In contrast, observational studies, which include cohort studies, case-control studies, case series, and case reports, describe the natural history or incidence of disease or analyze associations between risk factors and the outcomes of interest. As one might expect, there is generally a direct correlation between the complexity of a study design and the quality of the resulting data (Table 10.1).

Experimental studies

Randomized controlled clinical trials

The randomized controlled clinical trial is perhaps the most complex of the experimental study designs and is the standard to which all others must be held. The design of the randomized controlled trial evolved over the course of many years and each component of the design attempts to minimize the influence of study bias and confounders on the results. The ultimate goal is to create a sample population that is truly representative of the whole. In this way, the results of a limited trial can be generalized to the population at large with confidence.

According to the National Institutes of Health, clinical trials are conducted in four phases, each serving a different purpose and helping researchers answer different questions (Table 10.2). In phase I, researchers evaluate an experimental drug or intervention in a small number of test subjects (20–80) to evaluate its safety, determine a dose–response curve, and identify potential side-effects. In phase II, the experimental drug or intervention is given to a larger group of subjects (100–300) to test its effectiveness and further evaluate its safety profile. In phase III, the experimental drug or intervention is given to a much larger group of subjects (1000–3000) in order to “confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely”. In phase IV, post-marketing surveillance is continued to identify additional information on the risks, benefits, and optimal use of the intervention.¹⁰

Unfortunately, randomized controlled trials are expensive and often impractical to answer questions that compare one surgical intervention to another.^{11,12} While patients are often willing to be randomized to take a pill versus a placebo, few are willing to be randomized to one of two surgical procedures or to a sham procedure. Further, surgeons often have a strong preference for one type of surgery over another and are therefore unwilling to randomize patients.¹³

Although the randomized controlled clinical trial is considered the “gold standard”, it is not without limitations. For example, the underlying assumptions of randomized controlled clinical trials may be invalid. The preferable treatment between two alternatives may be unclear; evidence of treatment effects from other sources may be insufficient; only specific effects resulting from the intervention are therapeutically valid; and only when the trial’s inclusion and exclusion criteria match the characteristics of an individual patient can

Table 10.1 Levels of evidence

Level of evidence	Type of study	Key features
Level I	Randomized controlled trial	Two randomly selected groups, one serving as a control, with a blinded comparison of outcomes of an intervention
Level II	Prospective and retrospective cohort studies	A single group followed over time and evaluated for risk factors relative to outcome or incidence of disease
Level III	Case-control study	Two groups, one with and one without disease, with a comparison of risk factors relative to outcomes
	Well-designed clinical study	Experimental study design with an intervention and a control arm compared for outcomes
Level IV	Cross-sectional cohort study	A single group evaluated at a single point in time for disease prevalence or risk factors
	Case series	A single group of consecutive cases identified by a disease or condition and followed over time
Level V	Expert opinion	Opinion based on experience and review of literature
	Case reports	A small group identified by a disease or condition and followed over time

(Adapted from the American Society of Clinical Oncology.)

the outcome of the study be fully transferred to clinical practice.¹¹ In addition, randomized controlled clinical trials are inadequate to study infrequent or delayed adverse events; they are difficult, if not impossible, to conduct for the study of rare diseases; and although the benefits and harms of an intervention may be well recognized, its extent or significance is not always well assessed.¹²

Alternatives to randomized controlled clinical trials

In practice, randomized controlled clinical trials often pose logistical challenges and ethical problems, which limit sample sizes.^{14,15} Therefore, alternatives to randomized controlled clinical trials are needed.

Patient preference trials

When patients or surgeons have strong treatment preferences and refuse randomization, patients may be willing to participate in a preference trial. A preference trial is a trial in which the patient is offered the treatment options rather than random assignment. Patients who have a clear preference are given

their preferred treatment while patients without a preference are randomized.^{16–18} Thus both randomized and nonrandomized patients are studied together under the same protocol other than the treatment assignment.

There are a range of opinions as to the validity and usefulness of this study design. Some researchers believe they complement, rather than replace, randomized controlled clinical trials. Preference trials have been criticized for results that may not be generalizable due to the inherent bias in allowing patients with a strong preference to select their own treatment. Patients who prefer a specific treatment may be more compliant than others who have no such preference. This, and other potential impacts of a patient's preference on actual outcome, is not yet a well-understood bias that can be accounted for. In addition, particularly in small studies, there is the inability to control fully for potential confounders that may differ significantly between treatment groups.¹⁷ Proponents of preference trials believe that subjects who choose their treatment may be more representative of patients in actual clinical practice and that they can provide insights into the patient decision-making process.¹⁶

Large multicenter trials

When an insufficient number of patients are enrolled in a randomized controlled clinical trial, researchers may choose to use large multicenter trials to increase the sample size.¹⁶ A multicenter controlled clinical trial carries the same requirements as a single-center trial and each site must follow the same protocol, with identical inclusion and exclusion criteria, randomization strategies, interventions, and methods for collecting and evaluating the outcomes.¹⁴ Nevertheless, some researchers have found variability in surgery and surgical techniques in multicenter trials.¹⁶

Observational studies

Given the difficulty of executing a randomized controlled trial, the next best level of evidence is produced by a good experimental study or well-designed cohort study, with the

Table 10.2 Four phases of clinical trials

Phase	Purpose
I	To test an experimental drug or treatment in 20–80 people to evaluate safety, determine a safe dosage range, and identify side effects
II	To test the experimental drug or treatment in 100–300 people to determine effectiveness and evaluate its safety
III	To test the experimental drug or treatment in 1000–3000 people to confirm effectiveness, monitor side effects, compare it to commonly used treatments, and collect information to allow for its safe use
IV	Postmarketing studies to learn more about the drug's or treatment's risks, benefits, and optimal use

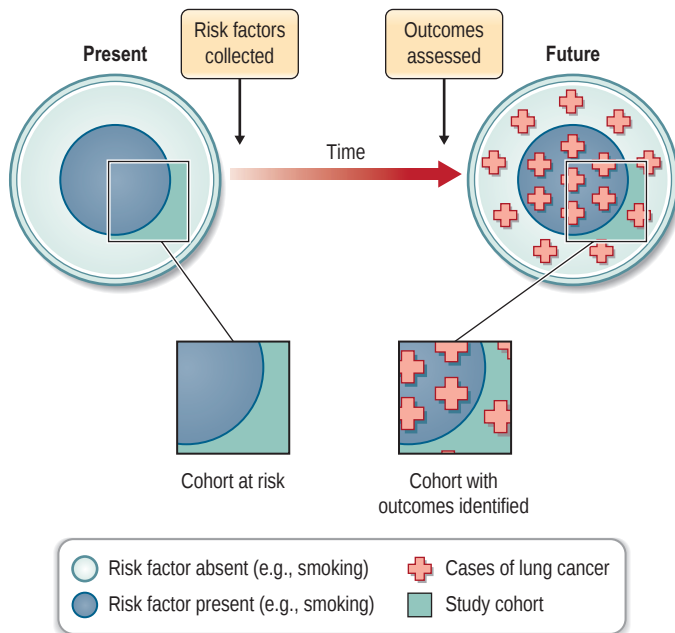


Fig. 10.3 In the prospective cohort study, the investigator develops a hypothesis about variables that may impact the outcome under investigation, collects data about those risk factors, and then follows the cohort for development of the outcome of interest. For example, when the association between smoking and lung cancer was suspected, a prospective study design increased the strength of that causal association. While prospective studies lend credence to causal associations, they are expensive and generally require years of follow-up.

former having some, but not all, the features of a randomized controlled trial. Although there is widespread belief that observational studies are less valid, often overestimating the magnitude of treatment effects, there are at least several reports suggesting that good observational studies can provide the same level of internal validity as randomized trials.^{19,20}

Cohort studies

Cohort studies evaluate a group or cohort at risk for disease. The evaluation may occur over time or at a single point in time. The latter is further described as a cross-sectional cohort study and is often used to collect data on the prevalence of disease. The second common use of cohort studies is to analyze the exposures that put subjects at risk for disease or interventions that reduce that risk. This requires an evaluation of the cohort at a minimum of two points in time. The study may be designed prospectively (Fig. 10.3) or retrospectively (Fig. 10.4). In the prospective cohort study, the investigator develops a hypothesis about variables that may impact the outcome under investigation, collects data about those risk factors, and then follows the cohort for development of the outcome of interest. For example, when the association between smoking and lung cancer was suspected, a prospective study design increased the strength of that causal association.

While prospective studies lend credence to causal associations, they are expensive and generally require years of follow-up. Retrospective studies have similar goals, but identify the cohort at risk in the present and investigate the risk factors or exposures that occurred in the past. This is often

done by subject recall or chart analysis, both of which are flawed when compared to prospective data collection. Data collected in this manner are more likely to be incomplete, inaccurate, inconsistent, or subject to recall bias. On the other hand, the major advantages of retrospective studies are that they can be done in a relatively short timeframe and are much less costly than prospective studies.

Case-control studies

Case-control studies (Fig. 10.5) differ from cohort studies in that two distinct groups of subjects are investigated. The first group (case) is selected by the presence of disease and the second (control) by its absence. In contrast, a single population at risk for disease is studied in a cohort design. Like cohort studies, the case-control design may be prospective or retrospective. The major strength of the case-control study is in the investigation of rare conditions or prevalence of disease and its increased susceptibility to bias. Controls may be concurrent or historic, matched (on key variables such as age and sex) or unmatched.

Case series and case reports

As defined above, cases are simply a collection of subjects that have been identified by the presence of a disease or condition. In our literature, these are frequently reported based on a specific intervention. If the collection of subjects is large and

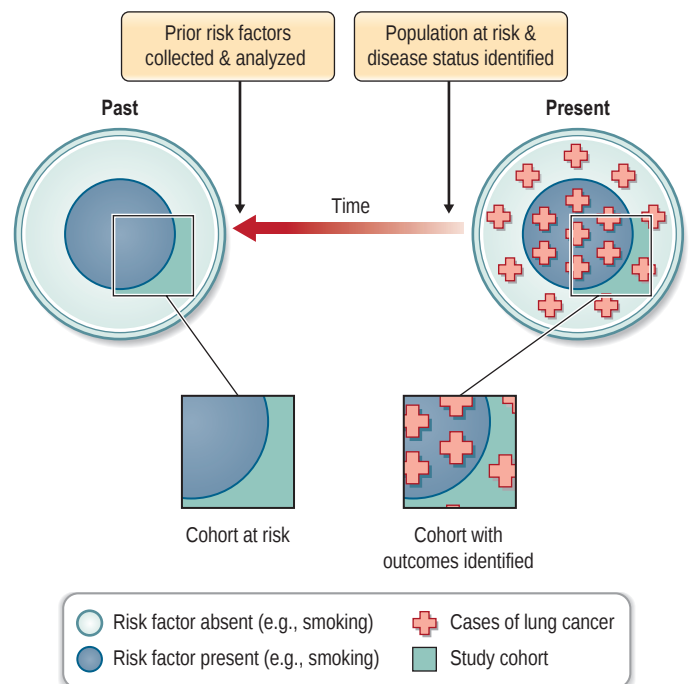


Fig. 10.4 In the retrospective cohort study, the investigator identifies a cohort, collects data about those exposures or risk factors that occurred in the past, and then examines the association between risk factors and outcomes. For example, when the association between smoking and lung cancer was suspected, a retrospective study design supported the hypothesis but failed to show a causal association. In retrospective studies, data collection is often done by subject recall or chart analysis, both of which are flawed when compared to prospective data collection. The major advantages of retrospective studies are that they can be done in a relatively short timeframe and are much less costly than prospective studies.

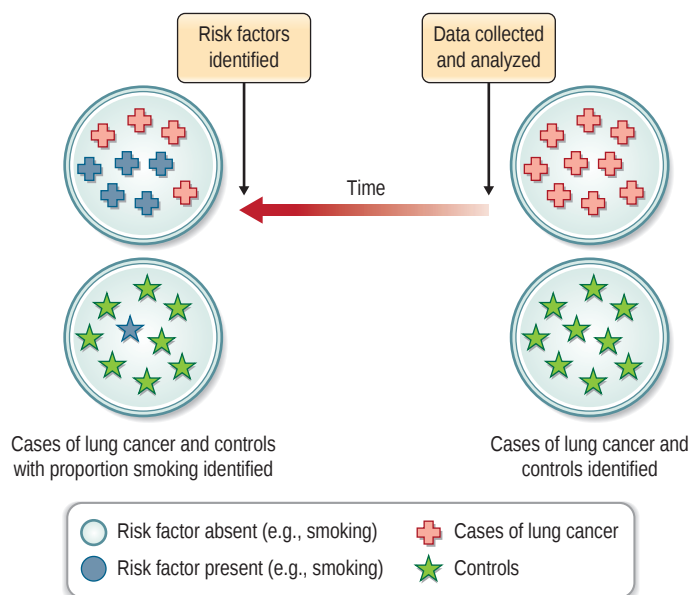


Fig. 10.5 Case-control studies differ from cohort studies in that two distinct groups of subjects are investigated. The first group (case) is selected by the presence of disease and the second (control) by its absence. Like cohort studies, the case-control design may be prospective or retrospective. The major strength of the case-control study is in the investigation of rare conditions or outcomes. Its weakness lies in the inability to assess incidence or prevalence of disease and its increased susceptibility to bias.

consecutive (case series), it may provide valuable information about indications and contraindications for surgery and expected outcomes. If the cases are nonconsecutive (case reports), it raises concerns about sampling bias, such as patient self-selection or surgeon's recall bias, that may dilute the ability of the study to capture the true indications and outcomes. The value of case reports lies in their ability to present a new idea, a new surgical approach, and refinement of existing surgical techniques and to communicate rare adverse events.

Large-database analysis

Population-based research

Effectiveness versus efficacy

Evaluating surgical outcomes is necessary in order to provide high-quality care, patient safety, and informed patient choice. Surgeons must have up-to-date reliable information about surgical risks and outcomes that can be transferable to their own patient population. Surgical outcomes data from single-surgeon or single-center studies demonstrate the efficacy of a procedure performed by a particular surgeon but do not provide data on the effectiveness of a procedure performed by different surgeons in diverse patient populations.

Clinicians need to have information on an intervention's outcomes under real-world conditions, not just in the optimal setting.^{21,22} As we discussed in the prior section, case series and clinical trials performed across a few academic centers are at risk for selection bias, and the results represent outcomes under optimal conditions. National databases, on the other

hand, include patients and physicians from all types of health-care settings, allowing assessment of outcomes in the "real world". This was demonstrated with the randomized clinical trials for carotid endarterectomy procedures (Fig. 10.6).²² The clinical trials reported a very low mortality rate for these procedures. However, after the clinical trials concluded, the mortality following carotid endarterectomy was substantially higher than that reported in the trials, even among those institutions that participated in the randomized studies. Mortality with carotid endarterectomy was also found to be inversely proportional to a center's volume. Thus, clinical trials generally do not represent real-world surgical outcomes.²² An alternative, research using a national database, is a population-based approach that provides information on a procedure's effectiveness under real-world conditions rather than just its efficacy in ideal situations.

The importance of power

Adequate sample size is another key component to outcomes research. True differences in outcomes can only be detected when research studies are adequately powered through a large-enough sample size.^{23,24} Plastic surgery faces the challenge of being a relatively low-volume group of providers compared to other specialties, such as those treating cardiovascular disease. Outcomes studies with small patient samples are often underpowered and at risk for a type II, or B, error. This statistical error happens when a study does not find a statistically significant difference between treatment groups when a difference truly exists (lack of statistical power).²⁵ Chung *et al.* found more than 80% of "negative studies" in the *Journal of Hand Surgery* had powers of less than 0.80 to detect a 25% difference between treatment groups. There was a greater than 20% risk of missing a true difference between treatment groups when a study had less than 0.80 power. The primary reason for the low power among these studies was insufficient sample size.²⁶ Large-database analyses can provide sufficient sample size to avoid an underpowered study.

Table 10.3 illustrates the importance of an adequate sample size in outcomes research. In this theoretical example, imagine

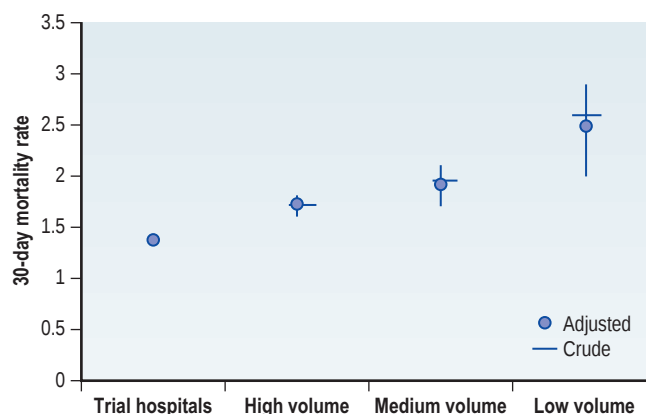


Fig. 10.6 Mortality rates following carotid endarterectomy in patients enrolled in a randomized controlled trial (trial hospitals) compared to those not enrolled in a study and operated on at hospitals with high, medium, and low volumes of endarterectomy cases. (Adapted from Wennberg DE, Lucas FL, Birkmeyer JD, *et al.* Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume and patient characteristics. JAMA. 1998;279:1278-1281.)

Table 10.3 Understanding the relationship between sample size and statistics

	Sample size	Number of complications	Complication rate (%)
Large physician group	48500	1500	3
Plastic surgeons	46	4	8
Difference is not statistically significant			
Large physician group	48500	1500	3
Plastic surgeons	46	0	0
Difference is not statistically significant			
Large physician group	48500	1500	3
Plastic surgeons	100	0	0
Difference is not statistically significant			

a large group of physicians having performed a cosmetic procedure on 48500 patients with 1500 complications (3% complication rate). Imagine a small group of plastic surgeons having performed the same procedure on 46 patients, and 4 had a complication (8% complication rate). This is not a statistically significant difference due to the small number of procedures performed by the plastic surgeons. Imagine, in a similar example, the complication rate for the large group of physicians remains at 3% (1500 patients with a complication) and, due to a slight change in sampling, the plastic surgeons had no complications on 46 patients (0% complication rate). This is also not a statistically significant difference because the study was underpowered in regard to the number of patients treated by plastic surgeons. In fact, the study sample could increase to 100 patients for the plastic surgeons with no complications and still there would not have been a statistically significant difference between provider groups.

Data sources

Clinical registries

Large databases in healthcare can be generally described as either a clinical registry or administrative claims data (Table 10.4). Clinical registries are designed for the purpose of collecting clinical data and have the advantage of providing detailed patient and treatment information. Many national clinical registries are disease-specific, such as the Surveillance Epidemiology and End Results (SEER) registry and the National Comprehensive Cancer Network (NCCN) that monitor outcomes in cancer patients. Plastic surgery has a national clinical registry called Tracking Operations and Outcomes for Plastic Surgeons (TOPS), which is supported by the American Society of Plastic Surgeons and the American Board of Plastic Surgery. The primary purpose of TOPS is to facilitate monitoring the quality of surgical care in plastic surgery. These types of clinical registries can be invaluable to researchers who are interested in studying patient populations that may not be captured in claims data, such as younger patients not captured in Medicare or self-pay cosmetic

patients. Researchers should be aware of the potential limitations of data sources. For example, the SEER registries only capture information within the first 4 months of initial treatment, and the TOPS database relies on voluntary physician-reported data. However, a recent study supports the validity of the TOPS database.²⁷

Administrative claims data

Administrative data, also known as “claims data” or “discharge data”, are collected for billing purposes and lack detailed patient information found in clinical registries. The data are available from several different sources, including hospitals, states, and payers. The content usually represents only one episode of care, unlike a clinical registry. The data are commonly in a uniform format called a hospital discharge abstract, which includes: a patient identifier, hospital identifier, demographic information (age, gender, race, payer), admission acuity (emergent, urgent, elective), length of stay, hospital charges, discharge status (death, transfer, extended care, home), primary/secondary diagnoses and procedures. Outcomes data from administrative sources are generally limited to mortality, length of stay, and charges. Data accuracy is better for primary procedure codes, diagnosis codes, demographics, and outcomes and less accurate for secondary diagnoses, which makes risk adjustment difficult.

It is not possible to use claims data to evaluate cosmetic procedures since these procedures are self-pay. Researchers have used information from CosmetAssure to evaluate cosmetic surgery outcomes.²⁷ CosmetAssure is an insurance policy sold nationally that covers medical and surgical complications from cosmetic surgery. There is a financial incentive to report a covered complication. However, clinical outcomes collected in the database are limited and patient-reported outcomes are not included.

How to use large databases for research

Administrative data can be a good starting point for a research project since the data are readily available and often inexpensive. The data source can also provide a large sample size that can help when studying a rare event or condition. The research question must take advantage of the strengths of the data for the project to be successful. Advantages of administrative data include population-based data that can be used to assess regional variations in care, real-world outcomes, and epidemiological trends.

Small-area variation

Prior to the 1970s, the rate of surgery for a population could not be determined, and data were limited to the number of cases performed at a given institution or by a specific surgeon. In 1973, Wennberg and Gittelsohn published a method for estimating the population served by a medical center, which allowed for the first time the calculation of procedure rates (e.g., the number of tonsillectomies per 100000 people served).^{28,29} We now know that certain surgical procedures demonstrate wide and unexplained variations in regional and national rates (e.g., hysterectomy, prostatectomy, caesarean section) whereas other procedures are performed at similar rates (e.g., appendectomy, cholecystectomy). In general, those procedures whose risks and benefits are well established

Table 10.4 Examples of clinical registries and administrative claims data

Data source	Description
Clinical registries	
Surveillance, Epidemiology and End Results (SEER) registry	Sponsored by the National Cancer Institute and collects data on cancer incidence and survival for approximately 26% of the US population (http://seer.cancer.gov/registries/)
National Comprehensive Cancer Network (NCCN)	Alliance of the leading cancer centers in the US that are dedicated to improving the quality of cancer care (http://www.nccn.org)
National Surgical Quality Improvement Program (NSQIP)	Program is sponsored by the American College of Surgeons and includes academic and private-sector hospitals which desire to participate. Data include inpatient and outpatient visits among patients undergoing major surgical procedures (https://www.facs.org/quality-programs/acs-nsqip)
Tracking Operations and Outcomes for Plastic Surgeons (TOPS)	Program is sponsored by the American Society of Plastic Surgeons, the Plastic Surgery Educational Foundation, and the American Board of Plastic Surgery. Board-certified plastic surgeons may participate. Inpatient and outpatient data are collected (https://tops.plasticsurgery.org)
Administrative claims data	
State–federal partnerships	State healthcare organizations submit datasets to the Agency for Healthcare and Research Quality (http://www.ahrq.gov)
State Inpatient Database	
Nationwide Inpatient Sample	
Kids Inpatient Database	
State Ambulatory Surgery Database	
Medicare¹⁵⁰	
Part A	Inpatient hospital discharge abstracts
Part B	Outpatient claims data
Veterans Affairs (VA) data	
Patient Treatment File (PTF)	Inpatient hospital discharge abstracts
Outpatient Care Files (OCF)	Outpatient visits at VA-based clinics
CosmetAssure¹⁵¹	Insurance company that covers complications related to cosmetic surgery

exhibit the least variability. Procedures with high variability suggest that the optimum management has yet to be established or adopted. Although small-area variations allow us to make observations about differences in procedure rates, they do not help explain these variations or tell us which rate is right. What it does suggest is that a more definitive evaluation needs to be undertaken to identify the optimal treatment strategy.³⁰ The Dartmouth Atlas of Health Care is one of the best examples of how to use administrative data to examine variations in the rates of surgery in the US using data from the national Medicare database, provider files, and American Hospital Association.³¹

Volume–outcome analysis

Another field of investigation that falls under the broad heading of large-database analysis is the area of volume–outcome studies. There is growing evidence to suggest that surgical outcomes are better at high-volume institutions.³² The reason may in part be due to the skill of the surgeon but also reflects the hospital and systems that support a given population of patients. A landmark paper by Birkmeyer *et al.*³³ described a significant correlation between surgeon volume and operative mortality in the US using Medicare

data. Another example is the work by Roohan *et al.*³⁴ on the 5-year survival of patients with breast cancer treated at low-, moderate-, and high-volume centers (Table 10.5). This work shows that there is as much as a 30% difference in the 5-year survival between low- and high-volume hospitals. In plastic surgery, the volume–outcome relationship has been analyzed for autologous breast reconstruction, identifying that centers with higher volumes have lower likelihood of complications.^{35–37}

Table 10.5 Volume–outcome association for 5-year survival after breast cancer treatment

Hospital volume	Breast cancer cases/year	5-year survival risk ratio
Very low	1–10	1.60
Low	11–50	1.30
Moderate	51–150	1.19
High	>150	1.00
(Adapted from Roohan PJ, Bickell NA, Baptiste MS, et al. Hospital volume differences and five-year survival from breast cancer. <i>Am J Public Health</i> . 1998;88:454–457.)		

Large cohort studies

Large-database analysis has played a key role in cohort studies. This allows relatively rare events to be analyzed with a large sample size, giving greater statistical significance and power to the analysis. It often involves linking multiple databases to examine risk factors or exposures relative to outcomes. The outcomes measured most often are mortality and cancer, as both are frequently tracked through various regional and national registries.

Epidemiology

Large databases are also useful tools to evaluate trends over time in surgical utilization and outcomes for a population. For example, the Nationwide Inpatient Sample (NIS) was used to document a dramatic increase in the use of bariatric surgery in the US.³⁸ The national SEER database has been used to assess sociodemographic differences in receipt of postmastectomy breast reconstruction³⁹ and assess trends in the use of breast reconstruction after the Women's Health and Cancer Rights Act.⁴⁰ Initial studies found that the overall use of breast reconstruction across the US was low, and that race/ethnicity is a significant predictor of receipt of postmastectomy reconstruction. More recent studies, using the NIS database, have shown that the rate of immediate breast reconstruction increased from 20 to 38% from 1998 to 2010, with a shift in the method of reconstruction from autologous to implant.⁴¹

Examples of large-database analyses in plastic surgery

Many large national and state databases have had limited applications for plastic surgeons.^{42,43} The most obvious reason is that many of the procedures performed by plastic surgeons are not captured in these databases. For example, the Medicare database captures only patients older than 65 years who use Medicare as the primary payment mechanism.

Several authors have used these databases to garner information useful to plastic surgeons. Gittelsohn and Powe used data from the state of Maryland to compare rates of elective surgery, such as septoplasty, rhinoplasty, reduction mammoplasty, and blepharoplasty.⁴⁴ Significant variations were noted in rates of surgery. Explanatory variables were explored, and the authors concluded that income and race were significant predictors of surgery. Keller *et al.* have looked at variations in the rate of surgery for carpal tunnel syndrome in the state of Maine.⁴⁵ They were able to identify a 3.5-fold difference in rates, and the authors concluded that the major driving factor is physician decision-making. We do not know the "right" rate of carpal tunnel surgery, but the data provided by studies such as this will enable us to begin to ask the appropriate questions.

Large databases have provided the source for cohort investigations on the relationship between breast reduction and a reduced risk for development of breast cancer. Boice *et al.*⁴⁶ identified breast reduction patients in Sweden using hospital discharge data linked with Swedish registries for cancer, death and emigration, and compared results with expected breast cancer incidence in the general population using the Swedish Nationwide Cancer Registry. The investigators found that women 7.5 years after reduction mammoplasty were at a statistically significant 28% decreased risk of cancer. The

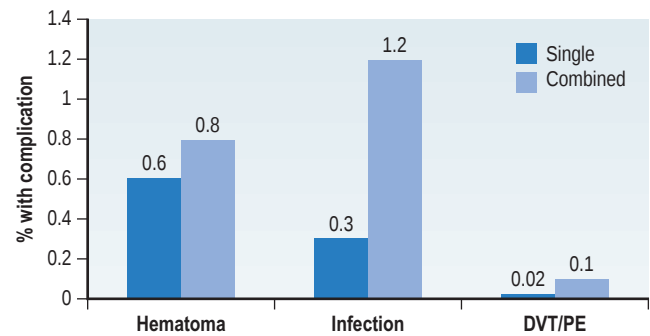


Fig. 10.7 The graph displays differences in overall complications for breast augmentation between single and combined procedures in the Tracking Operations and Outcomes for Plastic Surgeons database. Complications for combined procedures represent overall rates of a complication and cannot be assigned to a particular procedure. The rates of all the complications between single and combined procedures were significantly different ($P < 0.01$) using Pearson chi-square. DVT, deep venous thrombosis; PE, pulmonary embolism.

NCCN database has been used to evaluate the association between postmastectomy breast reconstruction and the delivery of adjuvant chemotherapy for breast cancer patients.⁴⁷ The authors found that immediate postmastectomy breast reconstruction does not appear to lead to omission of chemotherapy, but it is associated with a modest, but statistically significant, delay in initiating treatment. Breast reconstruction trends have been investigated using the NIS database. The authors identified increasing use of immediate reconstruction after the passage of the WHCRA in 1998, especially using implants. The increased use of implant-based reconstructions was associated with increasing bilateral mastectomies, especially for contralateral prophylactic mastectomies.^{41,48} Additional aspects of breast reconstruction have been studied, such as the association of sociodemographic variables with the method of breast reconstruction, the relationship between hospital volume and outcome for autologous reconstruction, and the economic implications of the use of microsurgery and bilateral flaps.^{35,49,50} Regarding cosmetic procedures, the TOPS and CosmetAssure databases have been used to assess outcomes with abdominoplasty and breast augmentation procedures.²⁷ The low complication rates found in this study support the safety of these procedures when performed by plastic surgeons. However, the authors stress that surgeons should be aware of the overall higher complication rates associated with combining breast augmentation with other procedures (Fig. 10.7). In summary, these represent just a few examples of the potential use of large databases in plastic surgery research.

Patient-reported outcomes research

Definition of terms

In plastic surgery research, attention is increasingly being placed on understanding the patient's perception of the surgical result and the impact that surgery has on quality of life (QoL). To appraise and demonstrate the benefits of a chosen surgical technique or alternate treatment adequately, it is important for plastic surgeons to understand the available approaches to measurement of patient-reported outcomes (PRO).

Patient satisfaction and QoL may be measured using specially designed questionnaires, known as PRO measures or PROMs. This term applies specifically to a questionnaire used in a clinical or research setting where responses are collected directly from patients. These questionnaires quantify QoL and/or significant outcome variables (e.g., patient satisfaction, symptoms) from the patient's perspective. PROMs provide a means of gaining insight into the way patients perceive their health and the impact treatments have on their QoL. A good PROM should evaluate the impact of disease, trauma, surgical or nonsurgical intervention on various aspects of a patient's day-to-day life in a manner that is scientifically sound and clinically meaningful.⁵¹

In plastic surgery research, many of the PROMs frequently employed in studies to evaluate surgical outcomes have not been developed and validated using acknowledged guidelines.^{51–54} Such PROMs are considered *ad hoc* questionnaires, and although they may pose clinically reasonable questions, one cannot be confident about their reliability (ability to produce consistent and reproducible scores) or validity (ability to measure what is intended to be measured). The use of such measures, however, has been extensive in plastic surgery. As an example, in a systematic review to identify PROMs developed for use with breast surgery patients, our team identified 65 *ad hoc* measures.⁵² PROMs that can be used in any patient group regardless of their health condition are called “generic questionnaires”, which allow direct comparisons across disease groups, or between sick and healthy groups. These measures can provide important information for health policy decisions. For example, research using the Short Form 36 (SF-36) – the most widely used generic measure in the world⁵⁵ – with breast reduction patients shows that women report clinically important differences in QoL compared with women in the general population.^{56–59} In the US, breast reduction is a procedure for which health insurance companies frequently dispute payment; it is thus useful to place the health burden experienced by women with breast hypertrophy into the context of patients with other medical conditions (e.g., women with hip or knee osteoarthritis seeking joint replacement).

However, there are limitations associated with the use of generic measures. Given their generic nature, they sometimes lack sensitivity to the particular concerns of a patient group. For instance, the SF-36, which measures physical, emotional, and social functioning, does not include questions about sexuality, body image, or satisfaction with breast appearance, which are clearly important concerns of breast reduction patients.⁶⁰ Generic measures, like the SF-36, may then not evaluate the most important issue for a particular patient group. Disease- or condition-specific questionnaires address problems specific to a single disease or treatment group. Such measures, when developed through in-depth patient interviews, can help to identify issues of importance to a specific group of patients. As these measures include content areas that are more relevant to a given patient group, they are more likely than generic measures to be sensitive to measuring changes in specific aspects of health. However, in general they cannot be used to make comparisons across different patient groups.

An additional challenge is that, in plastic surgery, there are many areas for which condition-specific instruments have been either inadequately developed or not developed at all.^{52–54} This situation is rapidly being remedied with the

development of new plastic surgery-specific questionnaires. As an example, the BRAVO study,⁶¹ which evaluated the effectiveness of breast reduction surgery, was conducted in 2001 using the Breast Reduction Symptoms Questionnaire. This questionnaire only provided an evaluation of symptom relief. Since then, the science of PRO measurement has evolved and new measures, such as the BREAST-Q,⁶² provide a comprehensive appraisal, including satisfaction with breast appearance and psychosocial well-being.

Essential elements for PROMs

PROMs must be clinically meaningful and scientifically sound. A questionnaire that is clinically meaningful addresses those issues considered important to patients and their surgeons. Scientific soundness refers to the demonstration of reliable, valid, and responsive measurement of the outcome of interest. A reliable measure yields consistent and reproducible results of the same measure. Reliability is an important property of a PROM because it is essential to establish that any changes observed between patient groups are due to the intervention or disease, and not to problems in the measure (Fig. 10.8). Test–retest reliability may be evaluated by having individuals complete questionnaires on more than one occasion over a time period when no changes in outcome are expected to have occurred. The degree to which individual responses remain the same is reported statistically as Cronbach's alpha⁶³ and intraclass correlation coefficients.⁶⁴

Validity is the ability of an instrument to measure what we intend it to measure (see Fig. 10.8). The distinction between reliability and validity is important because, just as reliability does not imply validity, the inverse is also true. That is, a reliable measure will always yield the same score, but it may not be valid, as it may not necessarily measure what it is meant to measure. Establishment of validity may be considered an ongoing process. The measure is looked at from various perspectives, including an assessment of the development process, consideration of known group differences, evaluation of internal consistency and of convergent and discriminant validity relative to other existing measures.

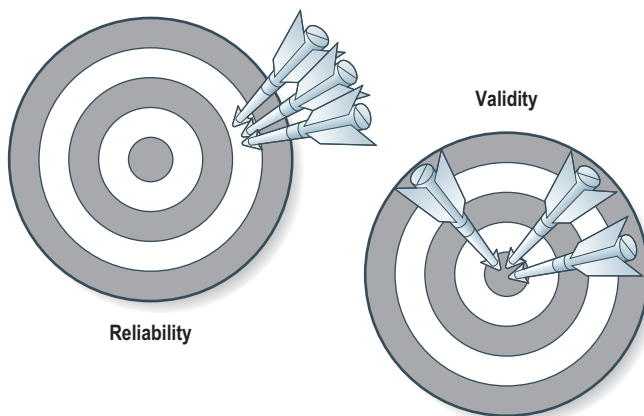


Fig. 10.8 Reliability and validity. The quality of any standardized survey is judged by its reliability and validity. The reliability is traditionally measured by test–retest; the validity is a measure of accuracy. Looking at it simplistically, reliability is the ability to hit the same spot repeatedly on the target, whereas validity is the ability to hit the bull's eye repeatedly.

Responsiveness is defined as the ability of a measure to detect significant change accurately. If a PROM is used to evaluate changes as the result of a surgical procedure or to follow patients over time, the measure must be sensitive to change. Responsiveness is examined by measuring outcomes, before and after an intervention, and by evaluating the measure's sensitivity to change.

Overview of PROM development

To choose a QoL measure for use in a study or in clinical practice, prospective users should take into account the process used to develop PROMs. Knowing how a PROM was developed is crucial to choosing an appropriate measure. Not infrequently, researchers choose questionnaires based simply on whether or not they have been "validated" and ask few questions about how the items for the questionnaire were constructed and tested. A poorly constructed or *ad hoc* questionnaire may be deemed "validated" simply because it has been used in various studies and some basic statistical evidence has been supplied. Frequent use of a questionnaire does not equate with quality nor improve its psychometric properties. Rather, to ensure that a PROM will ultimately prove to be a reliable, responsive, and valid measure, a rigorous step-by-step development process is essential. During the development process, careful qualitative work is necessary to conceptualize, map out, and operationalize the variables most relevant to patients. PROMs that are developed based on expert opinion alone cannot be expected to address all satisfaction and QoL issues that patients find relevant. Thus, while expert opinion is clearly valuable, patient interviews and focus groups are essential sources of information.

Since the early 1990s, there has been increasing international consensus regarding appropriate methods for the development and validation of QoL measures, culminating with the 2002 report by the Scientific Advisory Committee of the Medical Outcomes Trust⁶⁵ and more recently with the US Food and Drug Administration recommendations.⁶⁶ Cano *et al.*⁵¹ summarized these guidelines in a three-step approach to PRO measure development that involves procedures for item generation, item reduction, and psychometric evaluation. We have added a fourth step representing the ongoing process of instrument improvement (Fig. 10.9).

In the first step, the conceptual model to be measured is formally defined, and a pool of items is generated. These items for a PRO measure are developed through the following three sources: review of the literature, qualitative patient interviews, and expert opinion. The item pool is developed into a questionnaire which is pretested or pilot-tested on a small sample of patients in order to clarify ambiguities in item wording, confirm appropriateness, and determine acceptability and completion time.

In the second step, the PRO measure is field-tested using a large sample of patients. The questions that represent the best indicators of outcome are then retained in a shortened version of the PRO measure based on their performance against a standardized set of psychometric criteria. The research team's objective is to choose the best items from the field test measure for inclusion in the final measure. Items are eliminated according to tests of item redundancy, endorsement frequencies, missing data, factor analysis, and scaling assumptions. Acceptability, reliability, validity, and responsiveness are also

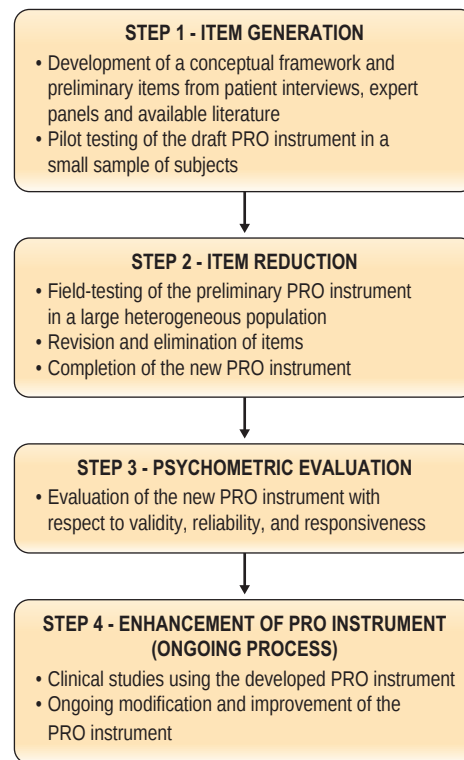


Fig. 10.9 Four steps of patient-reported outcome (PRO) measure development.

considered. The process completes questionnaire development and provides the first evidence of validation.

In the third step, further psychometric evaluation and validation is performed. This step involves the administration of the item-reduced questionnaire to a large population of patients to determine acceptability, reliability, validity, and responsiveness.

The fourth and final step involves the ongoing modification and improvement of the instrument. As an example, building upon the existing four modules of the BREAST-Q, a new procedure-specific module was recently developed for breast-conserving therapy (BCT) patients. This module facilitates comparisons between treatment groups (e.g., BCT versus mastectomy and reconstruction) and evaluations of new surgical approaches (e.g., oncoplastic surgery, fat grafting).

Our research group's development of the BREAST-Q illustrates how new PROM can be constructed. In phase I, a conceptual framework to understand patient satisfaction and QoL in breast surgery patients was developed and included six domains: satisfaction with breasts, overall outcome, and process of care, and psychosocial, physical, and sexual well-being. Our team developed this conceptual framework and set of items to measure each component of the framework using in-depth interviews and focus groups with patients, expert panels with plastic surgeons, and a review of the literature.⁶² We then performed pilot testing and cognitive debriefing to ensure that our PROM addressed all relevant issues and that the items were acceptable to patients and easily understood. In phase II, we performed an extensive multicenter field test with 1950 patients. Based on these data, item reduction and scale development were performed using modern psychometric methods. In this process, approximately 60% of the items were deleted. In phase III, the item-reduced measure

(BREAST-Q) was completed by another large sample of breast surgery patients and the data were examined to determine how the measure performed. More specifically, targeting, reliability, convergent validity, discriminant validity, and responsiveness were examined.⁶⁷

Modern psychometric methods

The science underpinning the testing of the attributes of reliability, validity, and responsiveness is known as psychometrics. The most commonly used form of scale evaluation, and the one most familiar to surgeons, is based on traditional psychometric methods.⁶⁵ However, in recent times, researchers have become aware of the limitations of these methods and are now moving to newer techniques. As such, modern psychometric methods such as Rasch measurement⁶⁸ and item response theory (IRT)⁶⁹ are increasingly being used in the development of PRO measures. Rasch and IRT methods were first developed for use in educational testing. While traditional psychometric techniques provide ordinal-level data, Rasch analysis provides interval-level data.⁶⁸ Ordinal-level data provides only a rank order (e.g., first, second, third). In contrast, with interval-level data, one unit on the scale represents the same magnitude measured across the whole range of the scale (e.g., degrees Celsius). This improves the accuracy with which we can measure clinical change. In addition, these methods provide estimates for patients (and items) that are independent of the sampling distribution of items (and patients). Among other benefits, this allows for accurate estimates suitable for individual-person measurement. This can help to inform patient monitoring, management, and treatment directly. Other advantages include item banking, scale equating, computerized scale administration, and the handling of missing data.^{70,71}

In the coming years, one may expect that these newer, more clinically amenable techniques will supersede traditional approaches to developing and testing PROM. Additionally in the near future, one may anticipate that electronic capture of PRO data will become widespread. As web access has become more prevalent throughout the world, it is possible for patients to complete questionnaires via the internet and even smartphones, which allow for real-time reports to both clinicians as well as patients.^{72,73} This has important implications for how PRO data may be used to inform clinical care. For research studies, the collection of ePRO data is also attractive as costs per patient are potentially reduced.

Utilities and preference-based measures

Key concepts

While PRO measures can provide valuable information on the way patients perceive their health and the impact treatments have on their QoL and other significant outcome variables, these measures do not incorporate patient preferences in their scoring systems.

“Preference” is a broad term used to describe the concept of desirability of a set of outcomes. Values and utilities are two different types of preferences, depending on which method is utilized to measure the preferences: values are measured under conditions of certainty (rating scale, time trade-off method), whereas utilities are measured under

conditions of uncertainty (standard gamble method).⁷⁴ Hence, a value or utility is a measure of preference for a particular health state or health service: the more preferable an outcome, the more value or utility is associated with it. The most common preference metric used is quality-adjusted life years (QALYs).

QALYs represent a measure of the dollar cost of a year of life if a person suffers one or more limitations of various kinds and degrees, taking into account both QoL and life expectancy.⁷⁵ QALYs can be estimated using a variety of evaluation tools such as the standard gamble, the time trade-off, or visual analog scales.^{75,76} Preference-based measures incorporate the strength of patients’ preference for the condition or disease, and the units of measurement range from 0.0 (i.e., death) to 1.0 (i.e., perfect health), the idea being that a year in perfect health is worth more to the patient than a year spent with a disability (Fig. 10.10). Importantly, some health states may be considered worse than death and thus have negative scores. Preference-based instruments thus take into account values and/or utilities in addition to QoL, and can be used in economic evaluations to aid resource allocation decisions.⁷⁷

There are two general approaches to measuring values and utilities. The first involves use of preference classification systems in which responses to a generic health status instrument are converted to a value or utility. This conversion is computed by an algorithm developed from population-based responses. Widely used preference classification systems include the Quality of Well-Being Scale,^{78,79} the McMaster Health Utilities Index,^{80–82} and EuroQol.^{83,84} Whereas preference classification systems are useful to study general health status and population health, they may not capture adequate

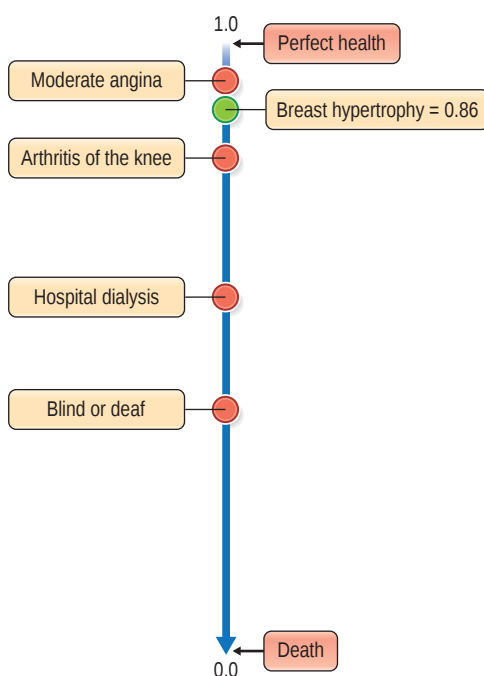


Fig. 10.10 Comparison of health states on a common utility scale. Utilities range from 0 to 1, where 0 represents death and 1 represents perfect health. Utilities differ from standard questionnaires in that they quantify quality of life with a single measure that encompasses the physical, psychological, and cultural preferences of the patient. This permits comparison between patients and across different diseases on a common scale.

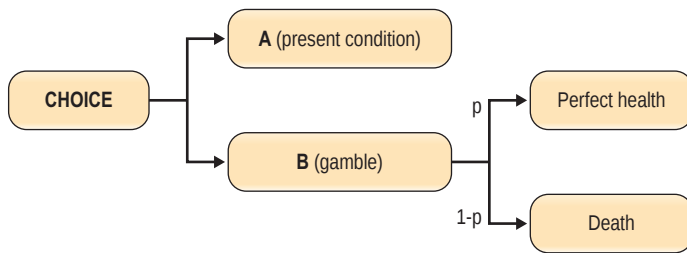


Fig. 10.11 Utility assessment with the standard gamble technique. In standard gambles, patients are asked to make a choice between two alternatives. One alternative is to remain in their current health, and the other is to accept a gamble with a chance of success and failure. The chances of success and failure are varied systematically until the point of indifference between the two choices is reached. The probability of success at this point of indifference is the utility value. Typically, the worse the perceived health of the patient, the lower the utility.

information about specific conditions or individual patient preferences.

The second approach to measuring values and utilities is to assess them directly. Several techniques may be used, including a visual analog scale, time trade-off, and standard gamble.⁷⁶ The standard gamble is considered to adhere most closely to the von Neumann–Morganstern utility theory. In this technique, patients are asked to make a choice between two alternatives. One alternative is to remain in their current health state, and the other is to accept a gamble with a chance of success or failure (Fig. 10.11). The chances of success and failure are varied systematically until the point of indifference between the two choices is reached. The probability of success at this point of indifference represents the value or utility estimate. Typically, the worse the perceived health of the patient is, the lower the value or utility score (see Fig. 10.10). Whereas the concept of preference assessment holds great promise for plastic surgery,^{85,86} measurement of values and utilities is an evolving science. Controversy exists as to the gold-standard technique for measurement, and alternative techniques may give slightly different results.^{87,88}

Comparative effectiveness analysis

Definition

The primary purpose of comparative effectiveness research (CER) is to facilitate value-based medicine, which is the practice of medicine based on the value conferred by a healthcare intervention. Depending on the definition used, CER may or may not have a cost component in the analysis. There is no standard definition for CER and study design may vary depending on whose perspective is taken: patient, payer, societal.⁸⁹ The total value or utility gained is measured in QALYs and calculated by multiplying the years of utility gain by years of benefit duration. This total gain, or comparative effectiveness, can be compared with that of any healthcare intervention, no matter how disparate. The concept of CER in healthcare is similar to the consumer rating reports by Zagats for restaurants and consumer reports for cars.⁹⁰

There is currently no standard definition for CER. Most researchers use the following definition for comparative effectiveness by the Institute of Medicine: “Comparative effectiveness research is the generation and synthesis of

evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition, or to improve the delivery of care. The purpose of comparative effectiveness research is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve healthcare at both the individual and population levels.”⁹¹ The analytic tools for data collection can include systematic reviews of evidence, modeling, retrospective analyses of databases, and prospective trials. Controversy surrounds the use of randomized controlled trials for CER because the research setting should demonstrate an intervention’s outcome under “real-world” situations rather than under optimal conditions (as demonstrated in Fig. 10.6).⁹⁰ However, the Institute of Medicine’s definition of CER does not reject the inclusion of randomized controlled trials.^{90,92}

National research priority

Reforming the national health system is a top priority for health policy leaders and the key aim is to control healthcare costs without impairing quality. Regional variations in treatment patterns and cost growth support the need for more informed medical decision-making.⁹² Many believe that this goal will only be reached if we have better evidence to inform healthcare decisions. Better evidence can improve quality, safety, and the effectiveness of healthcare by providing both patients and providers with the information needed to make healthcare choices.^{92,93} PCORI (Patient-Centered Outcomes Research Institute) was created in 2010 as an independent nongovernmental, nonprofit organization, to fund comparative clinical effectiveness research that addresses questions and concerns more relevant to patients.⁹⁴

Complexities

Whose perspective to take?

A variety of perspectives can be taken when examining the value of a healthcare procedure, ranging from the individual to society. The four most common perspectives evaluated are societal, patient, employer, and payer.⁹⁰ The societal perspective includes all of the benefits and costs associated with a treatment for the whole of society, rather than for just one individual patient. This type of analysis includes societal components such as work productivity and caregiver costs. The patient perspective only includes the costs and benefits of a treatment that impact the individual patient. Any increased productivity that would benefit a company or workplace situation would not be included. Productivity that directly benefited the individual would be counted. Costs included would be those paid out of pocket by the individual and costs related to travel and time off work.^{90,95}

An employer perspective only includes the benefits and costs of a treatment that impacts the employer. Any benefit from increased productivity by the employee is included. In addition, any tangential increased productivity is included, such as decreased sick leave from the other employees as a result of a vaccination. Costs included are out-of-pocket costs for the employer and lost productivity as a result of employee absenteeism.^{90,95}

The payer perspective includes the benefits and costs of a treatment that impact a payer only. Benefits to the individual

are not included. Increased productivity to the individual or society is not included. The time horizon used to calculate the benefits and costs is the expected length that the individual will participate in the insurance plan.^{90,95}

Types of economic studies

CER may or may not include cost when comparing treatments. However, there are five primary economic analyses in healthcare that compare treatments by costs and outcomes and differ primarily by how outcomes are measured. Firstly, cost-benefit analysis compares the net costs and net benefits of two treatments. Outcomes must be converted to monetary units, such as willingness to pay. The results are typically expressed as dollars expended for dollars gained.^{95,96} Secondly, cost-effectiveness analysis (CEA) measures the cost associated with two or more medical interventions for a given health state to determine the relative value of one intervention over the other. With CEA, the healthcare provider is looking to answer the following question: “What are the costs associated with the different treatment options available to achieve this goal?”⁷⁵ In a CEA, the health effects are measured in natural units directly related to the goal of interest associated with the intervention. For example, the measure of primary effectiveness can be expressed in terms of “cost per unit of effect”, where the effect can be the cost of life-years saved by kidney transplantation compared to dialysis,^{90,95,96} the average blood pressure decrease in mmHg, or the number of successful replantations.⁹⁷ Thirdly, cost-utility analysis (CUA) was developed to address the limitations of CEA. It has emerged in recent years as the preferred method for economic evaluations in healthcare because both the QoL and length of life must be assessed.^{75,90,95-98} Overall, CUA and CEA share similarities from the cost analysis perspective. However, they differ in terms of outcomes: in CEA, outcomes are single and specific to the medical intervention under study; in CUA, outcomes can be single or multiple, and, most importantly, consider the notion of preference.⁷⁴ The analysis produces a cost per QALY for the intervention that can be compared to other procedures. Fourthly, cost consequence analysis does not convert outcomes to a common metric but instead lists all of the consequences of the treatment.^{90,95} Lastly, cost minimization analysis is used to compare the costs of procedures when the outcomes are identical. This approach is rarely performed because two procedures usually have something different in regard to issues such as complication rates, pain, and time of recovery.^{90,95,96}

A controversial issue is whether costs are appropriate outcomes in CER. The primary justification for including costs is that the overall value of an intervention can be easily understood in economic terms.⁹² However, CER may conclude that the more expensive treatment has the best value. An example is breast cancer screening in patients with *BRCA* genetic mutations. In a study by Plevritis *et al.*, magnetic resonance imaging screening was found to be cost-effective relative to mammography.⁹⁹ CER looks at the benefits, not just the costs, and therefore identifies the treatment with the best value, not necessarily the one with the lowest cost.⁹² A cost-effectiveness analysis in breast reconstruction used the BREAST-Q as the effectiveness measure to analyze whether implants or autologous reconstructions were more cost-effective from the payer perspective. Autologous

reconstruction, all things considered, was a cost-effective option compared to implants when the expected lifespan of a patient was long (i.e., young women or early-stage breast cancer).¹⁰⁰

Study design

As previously discussed, there are two broad categories of research design: experimental and observational studies. Observational research has many advantages, such as speed, real-world decision, large sample sizes, and low cost. Experimental studies, such as randomized clinical trials, can overcome some of the limitations of observational studies by randomly assigning patients to different interventions, thereby controlling for known and unknown confounding factors. The Institute of Medicine’s recommendations are for the national CER program to develop large-scale, clinical and administrative data networks to facilitate the use of observational and experimental data to inform CER.⁹³

Limitations

There are several potential limitations to the implementation of CER in healthcare. For one, there is no standard definition for comparative effectiveness. It is also unclear what impact this type of research will have on healthcare since many providers do not incorporate this type of information into medical decision-making. Population-based study results may not be applicable to individual patient needs. For example, autologous breast reconstruction may be cost-effective compared to implants but the final decision of the method of breast reconstruction needs to be made by the patient. Patient treatment self-selection may also affect comparative effectiveness results. A study that finds no statistically significant difference in treatment outcomes does not necessarily mean that there is no difference in outcomes. The lack of statistical significance may be due to flaws in the study design, such as an underpowered study. Furthermore, different perspectives such as societal, patient, and employer may have different results. It is important to understand that CER helps to inform a medical decision but does not provide a simple “one size fits all” answer.⁹⁰

Summary

The primary reason for the interest by patients, providers, and health policy leaders in CER is the belief that better information will translate into better decisions and improved health outcomes. The long-term impact of these efforts will depend on healthcare reform legislation, the medical profession’s ability to encourage physicians to change practices, and patients’ willingness to participate in shared medical decision-making.⁹³

Future trends

Multicenter clinical trials network

When choosing a treatment option for their patients, plastic surgeons use many sources of information to determine best practice. Understandably, surgeons tend to rely in large part on their training and personal experience. Outcome studies

reporting “single-surgeon experience” have traditionally predominated in the plastic surgery literature. While such series are of value, their findings are not necessarily generalizable to other settings (e.g., lower-volume practices).

One of the more powerful forces in shaping best practice is the randomized clinical trial. However, in certain settings, single-center trials may be difficult to conduct because of limitations in sample size and resources. One way of preserving the clinical relevance of a trial is to have multiple institutions enroll, treat, and follow patients under a common study protocol. This approach also increases the heterogeneity of the population, which may ultimately lead to study findings that are more generalizable and relevant. This heterogeneity may however make it more difficult to detect treatment differences. Compared to a single-center trial, a treatment effect may be more difficult to detect in a multicenter trial. However, those effects that are detected are likely to be more convincing than those found in a single, homogeneous population.

To facilitate such studies, the Plastic Surgery Education Foundation established the Clinical Trials Network. This initiative has provided a mechanism by which plastic surgeons across the country may collaborate and contribute to the advancement of clinical knowledge. One compelling example of the value of multicenter clinical trials in plastic surgery is the Venous Thromboembolism Prevention Study. In this study, performed under the direction of the Network, five high-volume plastic surgery centers have adopted a common protocol for perioperative chemoprophylaxis of deep venous thrombosis. The incidence of venous thromboembolism is being prospectively evaluated and will be compared with the incidence of events occurring in a retrospective cohort of patients who did not receive prophylaxis. Data from this study will inform national recommendations for chemoprophylaxis, support the practice of evidence-based medicine and, ultimately, improve patient safety. One important barrier to multicenter trials in plastic surgery is the cost. Multicenter registries may be a more “cost-effective” form to evaluate outcomes and measure quality.

Knowledge translation

As clinical research in plastic surgery continues to advance rapidly, information overload is a constant challenge for surgeons. Incorporation of research findings into plastic surgery practice currently relies on publications in peer-reviewed journals and educational activities such as continuing medical education (CME) and continuing professional development (CPD). Because of their passive nature, CME and CPD have had limited effects on modifying physicians’ practice. Discrepancies or care gaps remain between what is recognized as evidence-based practice and the care provided in everyday plastic surgery practice. Moreover, patients may be receiving potentially harmful or unproven medical and surgical interventions. In a 2001 report entitled, *Crossing the Quality Chasm: A New Health System for the 21st Century*,¹⁰¹ the Institute of Medicine identified three main gaps in quality of care: medical error, overuse, and underuse. As an example, despite evidence that the risk of deep venous thrombosis is particularly high for patients undergoing combined abdominoplasty and liposuction, only 60% of plastic surgeons report use of thromboprophylaxis all the time.¹⁰²

The Canadian Institutes for Health Research (CIHR) is responsible for coining the relatively new term “knowledge translation” (KT) and defines it as “a dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health, provide more effective health services and products and strengthen the health care system.”¹⁰³ KT has been proposed as a solution to reduce care gaps, ensuring collaboration between the public, patients, clinicians, managers, and policy-makers to inform health-related policy and practice.^{104,105}

A model for understanding KT

The CIHR elaborated a Knowledge To Action model, further subdividing KT into two categories: (1) end-of-grant KT and (2) integrated KT.^{104,106} In end-of-grant KT, strategies are developed to match research findings to the needs of the appropriate individuals and organizations after research activity is completed. This approach is also known as diffusion and dissemination of research findings. Conversely, integrated KT engages individuals and organizations in every step of the research process, from establishing the research question to interpretation and dissemination of the findings. The goal of this approach is to produce research findings that are more likely to be relevant to, and used by, the stakeholders, including patients, clinicians, managers, and policy-makers.^{107,108}

A variety of models exist to improve quality of healthcare through KT. One of the most common is the 4T model. The first strategy, referred to as T1 (translation 1), focuses on transforming basic science findings into translational research. Next, T2 (translation 2) comprises all activities directed at producing clinical studies based on translational research findings. Activities under T3 (translation 3) center on the dissemination and delivery of healthcare interventions to all patients, in every setting of care. Finally, T4 (translation 4) activities focus on translating dissemination experiences into new basic science investigations.

Barriers to uptake

The healthcare system currently falls short in its ability to translate knowledge into clinical practice. A study comparing medical care in the US with established national guidelines, medical literature, and existing indicators of quality demonstrated that, overall, patients received 54.9% of recommended care.¹⁰⁹ In fact, it takes an average of 17 years for new knowledge generated by research, such as randomized controlled trials, to be integrated into widespread practice.^{110,111} In a systematic review of the literature by Cabana *et al.*, the sequence of behavior change in a physician’s clinical practice has been divided into three domains: knowledge, attitude, and behavior.¹¹² Each domain may encounter opposing forces to the application of evidence-based knowledge. Firstly, physician knowledge acquisition may encounter barriers such as lack of familiarity and lack of awareness (e.g., increasing volume of new literature, time invested to stay informed). Secondly, physician attitudes that favor behavior change may be deterred by the lack of outcome expectancy, self-efficacy, and motivation (e.g., mistrust regarding the validity of clinical research, skepticism about the applicability of evidence to clinical practice, discomfort regarding modification of previous practice). Lastly, factors hindering the practical

application of behavior change reflecting new research-based knowledge may be external (e.g., patient refusal, conflicting research evidence, lack of resources, organizational constraints).^{112,113} Other factors influencing successful implementation of evidence-based interventions include miscommunication between the organization and the healthcare providers, preventing identification of factors hindering compliance with recommended practices. Successful implementation of evidence-based practice has thus far depended on the adoption of a comprehensive program that incorporates methods to improve culture, teamwork, and communication.^{114,115} There is now a burgeoning field called the science of healthcare delivery.^{116–118}

Learning collaboratives

In a quest to improve healthcare delivery, the Institute for Healthcare Improvement developed a learning collaborative model in 1995, called the Breakthrough Series model. It is an ongoing learning process in which groups of practitioners from different healthcare organizations work in a structured environment to improve a chosen area of their practice.¹¹⁹

While clinical trials networks are designed to test an intervention (e.g., drug, surgical procedure, medical device, screening approach), quality improvement learning collaboratives focus on the best way to adopt, implement, and adapt evidence-based practice to real-life environments. These collaboratives often identify ways to improve quality and reliability and to decrease healthcare costs by meticulous comparisons of variation in care processes, culture, and systems between organizations.¹²⁰ Many successful collaboratives have come together around diverse health conditions such as cardiac care,¹²¹ cystic fibrosis,¹²² infant care,¹²³ central line infection,¹¹⁴ and a whole host of topics sponsored by the Institute for Healthcare Improvement.¹²⁴

In collaborative endeavors, the ultimate goal is to promote the dissemination and adoption of evidence-based practice to help organizations and healthcare professionals close the gap between actual and best practice in healthcare. Using adult learning principles, learning collaboratives allow practitioners to collaborate and learn from their collective experience and challenges. By bridging together practitioners with different roles in the same organization¹¹⁴ and from different organizations,¹²⁵ information is shared on best practices, quality methods, and experiences while implementing systematic improvements to the overall system of care.

In their systematic review, Schouten *et al.*¹²⁶ reported on the impact of quality improvement collaboratives, and concluded that the evidence is “positive but limited” and that further study is warranted to understand the most effective models. Hospitals or providers with worse outcomes could learn best practices of those with better outcomes. An example of this is the Michigan regional collaborative improvement program, funded by a private insurance carrier, that decreased surgically related complications in general, and vascular surgery in particular by 2.6% (2500 patients) with savings of approximately \$20 million.¹²⁷

What does this mean for plastic surgeons? Within plastic surgery, a pilot learning collaborative has been launched using TOPS as a central data repository.¹²⁸ The collaborative’s focus is on sharing practices around abdominal procedures and resultant seroma rates. A challenge for the plastic

surgery community is that a high percentage of surgeons practice alone in a private practice setting and may lack the resources needed to participate in such endeavors. In addition, the practice of plastic surgery takes place in a highly competitive marketplace where a culture of collaboration, rather than competition, may be a difficult, but not impossible, shift to enable. It is possible that outside forces such as changing reimbursement strategies will nudge our community towards recognizing the value in collaborative learning and improvement.

Role of electronic medical records/ integrating data collection into flow of usual care versus research

To have truly effective KT and continuous improvement in the quality, safety, and value of healthcare, an infrastructure that supports data use in clinically intelligent ways is paramount. Current systems are limited by use of paper and by lack of interoperability, even when electronic data are available, thus making the majority of clinical data relatively inaccessible in practical terms. Where clinical data are currently used, e.g., Surgical Care Improvement Project (SCIP)¹²⁹ measures and National Surgical Quality Improvement Program (NSQIP)¹³⁰, full-time employees must be hired to abstract data manually from paper or electronic records and re-enter them in a different format for submission. Due to these high labor costs, only a small sample of surgical cases and data points can be included. When clinical research trials are performed, much of the data collection is done on paper, duplicating information already present in the medical record, which again represents a very labor-intensive process. Furthermore, when patient-reported data are collected, patients may be asked to answer questions similar to those already asked during the clinical encounter, thus adding significant redundancy to patients as well. In addition, it can be challenging or even impossible to score paper-based questionnaires at the bedside, thus depriving the patient-provider relationship of data that could otherwise have a significant impact on their decision-making.

Several specialty societies, including the American Society of Plastic Surgeons, have hired consultants to design data collection websites such as TOPS. However, this typically requires practitioners to abstract data manually and re-enter it into the national database, thus creating a significant barrier to participation by many. Few groups, other than the Cancer Trialists Collaborative Group, which receives national funding, have been successful at carrying out and sustaining such efforts.

Possible solutions: generic

With the evolution of computer technology and the internet, the feasibility of turning data into meaningful information for activities such as decision-making at the bedside, physician feedback, benchmarking, improvement of care, credentialing, certification, and research is becoming much more affordable, practical, and realistic. Although information technology has much to offer in enabling the transformation of healthcare delivery, it has been slow in adoption and effectiveness compared to other industries. To stimulate growth, the federal

government has developed a 5-year plan to phase in and define “meaningful use” of electronic medical records (EMRs).^{131,132} The hope is that this will increase meaningful adoption of health information technology (HIT) by both providers and hospitals. The Medicare and Medicaid incentive program will provide incentive payments to hospitals or providers that implement, upgrade or demonstrate EMR technology. There is a three-stage plan for implementing the meaningful use of EMR from 2011 to 2016: data capture and sharing, advance clinical processes, and improved outcomes.¹³²

Standards for PROMs have not yet been included in the current and future proposed definitions of “meaningful use”. However, decision support rules and best practice alerts may well benefit from inclusion of these measures. For instance, a PRO instrument for depression could generate a best-practice alert for referral to a mental health professional.¹³³ Likewise, a PRO measure for domestic abuse could generate a best-practice alert for referral to social services professionals. Having such PRO measures integrated into the flow of care electronically, thus enabling immediate scoring and reporting to the healthcare team, advances our ability to provide high-quality care. This reaches beyond what we have been able to achieve in the past with paper-based and research measures administered and scored well after an office encounter, and often never reported back to the care team. For example, the International Consortium of Health Outcomes Measurement is a nonprofit organization that aims to transform healthcare by standardizing the way to measure outcomes. Their recommendations for measuring the value of care for individuals with cleft lip and palate include 9 dimensions of outcomes, four of which are captured with CleftQ.¹³⁴

The gradual adoption of EMRs by more and more health systems, practices, and individual practitioners provides a growing opportunity to capture structured data at the point of care. Not only can these systems facilitate the systematic capture of data, but they also allow systematic analysis and reporting. This reporting can be done with several purposes in mind, such as instantly providing decision support and best-practice evidence to providers at the time of patient encounter. The reporting can be “rolled” up to a cohort of patients with similar health conditions (e.g., all breast cancer patients), similar procedures (e.g., all free flaps), or on a provider’s panel (e.g., all surgical cases performed by the same surgeon). These reports could also be aggregated at the practice level, departmental level, or at the national level.

Possible solutions: plastic surgery and PROMs

It is often a challenge for plastic surgeons to mobilize the resources within their clinical environment to develop and program the tools to collect field-defined data specific to the specialty. However, several innovative centers have begun to do just that with PROM. Just as we have easy access to timely and standardized laboratory results, so should we have similar availability of timely and standardized PRO at the bedside. In many cases, particularly in the specialty of plastic surgery, PROM may provide us with better decision-making information, or may add an important dimension to more traditional biometric measures. For instance, the Levine score¹³⁵ for carpal tunnel patients, when available during an encounter, is very helpful to individual patients and their surgeons in quantifying the impact of the symptoms and in

tracking the effect of a particular treatment. Likewise, the BREAST-Q⁶² has been developed to provide useful bedside information as well as valuable research information.

At Dartmouth, we have been able to integrate electronic patient-reported intake and outcomes into routine care for the purpose of improving the quality and efficiency of care, reporting, and research. This has been operationalized across 30 clinical conditions including comprehensive breast care (BREAST-Q) and hand care (Quick Disabilities of Arm, Shoulder and Hand, Boston Carpal Tunnel Questionnaire). At Memorial Sloan-Kettering, the BREAST-Q is routinely administered at the point of care allowing for the clinical use of this information and implementation of interventions when needed. Plastic surgeons participating in TOPS can sign up to have the BREAST-Q sent to their breast patients for longitudinal postoperative tracking. A common sentiment expressed by practitioners who have access to these measures at the time of an encounter is that they cannot imagine ever returning to a practice style where this information was not available.

As we become more sophisticated at measurement, it becomes important that, as a community, we endorse and use the same measurement tools so that we can make meaningful comparison of the data through our national registry. There is no doubt that these measures will continue to improve through an ongoing iterative process. The more plastic surgeons participate, the more they can help shape the design of these data systems to make them even more practical at the bedside, and more effective at answering important clinical questions through well-designed research studies and learning collaboratives. The ICHOM (International Consortium for Health Outcomes Measurements)¹³⁴ organizes groups of physicians, researchers and patient advocates to define a standard set of outcomes measures, advocating for global adoption so providers can compare, learn and improve. This may promote international collaboration and decrease healthcare costs. Currently, they have 12 completed datasets (including cleft palate) but aim to have 50 by 2017.

What do we do with the outcomes?

EMRs and HIT have the potential to improve the quality of healthcare and support the transformation of the way medicine is practiced and provided to patients. Computerized continuous quality assessment from data found in EMRs should facilitate ongoing monitoring and improvement of healthcare quality as well as clinical decision-making. Numerous national initiatives are currently assessing ways to measure care systems with the goal of collecting and comparing data on the structure of healthcare systems, care interventions, and patient outcomes. These data are valuable to many stakeholders: patients, providers, healthcare payers, and government agencies. Thus, there is currently an unprecedented focus on quantifying healthcare value, because improving the outcomes of care at a more affordable price is an important and pressing challenge.

The first model summarizing factors influencing patient outcomes was developed by Donabedian in 1966.¹³⁶ This framework is still relevant today, and hypothesizes that care structures (e.g., dedicated microsurgical care team) and care processes (e.g., standard limb replantation care pathway) play

a role in patient outcomes. In this type of model, outcomes can take any form appropriate to one's practice: for example, mortality, health status, functional status, satisfaction, QoL, and cost.

The creation of clinical practice guidelines has become a strategy frequently used to improve healthcare quality and outcomes. They represent a way of outlining evidence-based practices through a review and synthesis of the literature in an attempt to guide patient care better. However, although extremely useful, guidelines alone are not sufficient to produce improvements in the quality of care. The strategy of publication and dissemination of practice guidelines has failed to guarantee their implementation, and there may be physician resistance as clinicians feel their autonomy is compromised. Also, clinical guidelines do not account for patient variability, but need to be updated very often since medical knowledge is continually changing. An alternative to clinical guidelines is standardized clinical assessment and management plans (SCAMPS): flexible and continuously improving care guidelines created by physicians, with the aims of decreasing practice variability, optimizing use of healthcare resources and improving patient care. SCAMPs allow physicians to adapt clinical pathways to individual patient needs by incorporating current scientific evidence but also including patient characteristics into the pathway. Since 2009, more than 12 000 patients have been enrolled in 49 adult and pediatric SCAMPs in nineteen institutions, with reduction of practice variability and improved patient outcomes.¹³⁷

Performance measures

In the process of facilitating the measurement of healthcare quality, performance improvement measures serve as a vehicle for translating the strongest clinical evidence into practice more rapidly. Measures typically go through many iterations before they are widely endorsed as being meaningful and reliable. In the earlier stages of maturation, it has been proposed that the measures be called "quality metrics".¹³⁸ These metrics can be used to assist providers, hospitals, or the healthcare system in self-assessment, enhancing both the quality of care and patient outcomes. With repeated improvements in the measures themselves, they may rise to the exacting standards of organizations such as the National Quality Forum¹³⁹ and be endorsed as formal "performance metrics"¹³⁸ and used for public reporting, comparison of care between institutions or healthcare providers, P4P initiatives, and for meaningful use initiatives. The credentialing and financial incentives behind compliance with performance metrics encourage healthcare providers and organizations to offer the strongest evidence-based quality of care.

One of the main examples of a process-driven quality initiative is SCIP.^{129,140,141} This national quality partnership of organizations was initially a voluntary collaborative to improve surgical care by reducing surgical complications. It transitioned to a mandatory, publicly reported system in 2005.¹⁴² The ultimate goal of this program was to reduce the incidence of preventable surgical morbidity and mortality nationally by 25% by the year 2010 through collaborative efforts. This program has four preventable complication modules: (1) surgical site infections;¹²⁹ (2) venous thromboembolism;¹⁴³ (3) cardiovascular events; and (4) respiratory

complications. The withholding of a pro-rated Medicare payment was used as a financial incentive to guarantee participation in SCIP. However, at present, studies evaluating the effect of SCIP process measures following colorectal surgery on surgical site infection rates have mixed results.^{144,145} Of note, these studies have relatively small sample size at each participating institution. Furthermore, SCIP measures of performance target a limited set of surgical procedures, none of which pertains to plastic surgery. Such measures are primarily useful at the organizational level, but not at the level of the individual provider. However, collection of SCIP measures from a data-rich EMR will make reporting at the individual provider level much more feasible.

The American College of Surgeons' National Surgical Quality Improvement Program (NSQIP)¹³⁰ is another initiative that is gaining increased traction amongst surgical specialties and hospitals to track and improve surgical outcomes. For participating hospitals, and the surgeons they represent, clinical data rather than administrative data can be used to compare outcomes across organizations and support improvement efforts. One of the flaws is that outcomes are reported only for the first 30 days, leaving insufficient time to analyze outcomes in some plastic surgery procedures.¹⁴⁶

To date, two studies addressing performance measures in plastic surgery have been conducted in the UK. The British Association of Plastic Surgeons, following a requirement of National Health Service clinicians to take part in clinical audits, has taken the initiative to identify surgical procedures that could be used as markers of performance across the specialty.¹⁴⁷ In their pilot study, a national performance assessment for pedicled and free-flap survival was completed. When comparing four plastic surgery units, the overall outcome achieved was 89% total flap survival. In 2011, the National Mastectomy and Breast Reconstruction Audit reported outcomes in more than 8000 women with mastectomy and reconstruction in the UK. The Breast-Q was chosen as one of the outcome measures. This study was useful to determine benchmarks, analyze level of satisfaction in patients with breast reconstruction, and identify providers with better and worse outcomes, amongst others.¹⁴⁸ The multicentre MROC study (Mastectomy Reconstruction Outcomes Consortium) is currently enrolling patients in 11 centers in the US, and it was designed to explore patients' experiences after reconstruction regarding aspects such as satisfaction with breasts, psychosocial well-being, postoperative pain, etc. Patient questionnaires are administered at several points (preoperative, one week, three months, one year and eighteen months), and the study is projected to close accrual in 2016. This important study will shed light on the patient's point of view regarding breast reconstruction method, timing, but also costs with the different procedures.¹⁴⁹

The Maintenance of Certification Program of the American Board of Plastic Surgery has ventured into this arena of physician performance measurement. Their Practice Assessment in Plastic Surgery (PA-PS) modules include 20 of the most common plastic surgical procedures. Some data analysis from this system has already found use.¹⁵⁰ Although far from being as robust as what will be needed in the future, these modules will likely undergo frequent upgrades to improve their usefulness to the practicing clinician and will undoubtedly include PRO in the future.

On another front, the Joint Commission that accredits healthcare organizations has created a standard around evaluation of professional practice at the individual provider level.¹⁵¹ Like other initiatives, preliminary measures will be derived largely from process data and perhaps surgical complications and we will await future iterations to integrate patient-reported outcomes.

Public reporting and P4P

Despite limited evidence on their benefits, public reporting of hospital quality data and P4P are the two most advocated strategies to accelerate improvements in healthcare quality and safety.¹⁵² Measuring and publishing information about quality of hospitals, health plans, and physicians are driving P4P programs. Public accountability of quality measures has proved an excellent motivator for healthcare providers and hospitals to invest efforts in quality activities, as performance measures are open to the public for review.^{153,154}

P4P is a compensation model used by private payers that links financial incentives to the quality of healthcare provided.¹⁵⁵ While the P4P concept is gaining momentum as a means of improving overall quality of care by reducing gaps between clinical practice and evidence-based guidelines, it is also viewed as a way of encouraging efficient use of healthcare resources. P4P initiatives can take various forms, encompassing different payment models, various stakeholders (e.g., hospitals, group practices, private practitioners), and diverse clinical conditions. The available evidence regarding the impacts of P4P has been mixed.^{156–158} Some large-scale studies report moderate enhancements in process-of-care measures, but to date, no impact has been reported on patient outcomes or efficiency of care.^{152,159–161} Pay for performance (value-based purchasing) is an important part of the Affordable Care Act, intended to financially incentivize hospital/provider performance. Scores reflect achievement compared to other hospitals, as well as yearly improvement. Value-based incentive payments will be given to providers who deliver higher-value care (e.g., fewer complications) and meet certain performance standards, as evaluated by different outcomes measures.¹⁶² Additionally, the US federal government has introduced its own Pay for Reporting (P4R) program: the Physician Quality Reporting Initiative. This initiative offers financial incentives to Medicare providers who participate in quality reporting. Unlike P4P programs, the P4R model compensates physicians regardless of their performance on process and outcome measures.¹⁶³

In 2002 and 2003, a natural experiment occurred, involving thousands of American hospitals participating in a national public reporting initiative, with more than 200 organizations engaged in a simultaneous P4P initiative. Lindenauer *et al.*¹⁵² observed that hospitals participating in both public reporting and P4P programs showed modestly greater improvements in healthcare quality than hospitals engaged in public reporting alone.

Some critics argue that little evidence links performance measures to patient outcomes.¹⁵⁴ One explanation for this may be found in the realization that current measures focus on a very small number of processes of care out of the total interventions that characterize the patient's experience in the hospital.¹⁵³ Also, results of randomized controlled trials with

homogeneous study samples may not be generalizable to all patients.¹⁵⁴ Besides, outcomes in daily practice are influenced by various amalgamations of patient and treatment variables, which are seldom replicable in randomized controlled trials. In addition, many of the studies that failed to demonstrate an improvement in outcomes did not assess outcomes occurring at longer intervals after the delivery of the process of care to the patient. Moreover, the present burden of comprehensive data collection limits investigators' ability to capture patient information between care settings over time. Data collection should be facilitated by the widespread use of electronic medical records, allowing researchers to evaluate long-term outcomes readily.¹⁵³

Decision aids for patients

Making an informed decision about the best treatment can be difficult for patients, especially when there is more than one medically reasonable option. Over the last 30 years, the field of evidence-based decision-making in healthcare has grown rapidly. Patient decision aids aim to support this process and help patients arrive at informed value-based choices. According to the International Patient Decision Aids Standards collaboration, decision aids are evidence-based tools designed to prepare patients to contribute actively to the decision-making process when choosing among healthcare options, according to their preferences and values.^{164–166} They differ from conventional patient education materials in that they are more detailed, specific, and deliberated, and they provide a more personalized focus on options and outcomes, with the goal of helping patients make informed choices. Decision aids for patients do not replace the patient–physician encounter; instead, they supplement the provider's counseling about healthcare options.¹⁶⁴ They can be used before, during, or after an interaction with a practitioner.

A recent Cochrane systematic review of patient decision aids reported that they improve patients' knowledge regarding their options, and reduce decisional conflicts from feeling uninformed or confused about personal values.¹⁶⁴ After using decision aids, fewer patients are ambivalent about their treatment choice. Importantly, more patients participate actively in the decision process. However, randomized controlled trials have failed to demonstrate that these tools improve patient outcomes such as decision uncertainty, satisfaction, anxiety, or QoL.¹⁶⁷ Moreover, there is scarce evidence on the effects of decision aids on patient compliance with treatment, decisional regret, litigation rates, healthcare costs, and resource use.¹⁶⁴

Evidence supporting the use of decision aids in clinical practice is substantial.^{164,167,168} A good decision aid should meet the needs of its target population, and be acceptable to both patients and providers who wish to incorporate them in their clinical practice. Barriers to successful implementation are the lack of effective systems for delivering decision support. Further research is needed to assess the effects of decision aids on congruence between patients' values and their chosen options.

Designing and building high-quality decision aids is greatly enhanced when the available evidence base, including patient-reported outcomes, is robust. There is much opportunity for the plastic surgery community to add to this evidence base.

Conclusions

This chapter would be incomplete without emphasizing the key take-home messages. A clinician cannot make good decisions without good evidence and cannot generate good evidence without good study design and good data. Maximizing patient care and surgical outcomes will require continuous efforts to identify information needs and to produce the best evidence to fulfill these needs. Outcomes research offers a broad spectrum of methods by which to obtain good evidence, and these have been insufficiently leveraged by our specialty. In particular, measuring the patients' perspective on outcomes is a crucial dimension of research and clinical

care that is underdeveloped and underutilized. Measuring outcomes is not just about the final result of our interventions but a means by which we gather evidence to improve decision-making, the processes of care, and the systems in which we work. Collaborative data collection through clinical trials and quality improvement initiatives is essential to the generation of clinically meaningful information in our specialty. Our decisions need to be based on the highest-quality evidence and not the accumulated experience of a single surgeon, even if that surgeon is truly expert in the field. Equally important to generating clinically meaningful information is to translate that information into practice by providing surgeons with mechanisms to implement and monitor new standards.



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Principles of cancer management

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SYNOPSIS

- There has been a gradual progression from radical to more conservative resections of many cancers.
- Neoadjuvant therapies have facilitated resectability and even down-staging of some tumors.
- A better understanding of immunology has led to the development of biologic therapies.
- Targeted therapies represent a new paradigm in the treatment of cancer aiming to combine efficacy and decreased toxicity.
- Rational, evidenced approaches to tumor ablation should aim to improve oncologic outcomes, reduce morbidity, and facilitate reconstruction.

Background

The introduction of reconstruction after extirpation was a major advance in cancer management. Plastic surgical techniques have facilitated large-scale resections by enabling immediate closure of surgical defects. Furthermore, development of microsurgical techniques enabled transfer of highly vascularized flaps from distant donor sites, thereby increasing the versatility of the reconstructive techniques and obviating the need for time-consuming surgical delay procedures or waltzing flaps.

Improved understanding of tumor pathobiology and prognostic factors has led to a gradual paradigm shift in cancer treatment from a “one size fits all” approach to tailored oncologic therapy. This chapter provides background for the current rationale behind modern treatment of tumors.

History of cancer treatment

While surgery remains the most successful single modality treatment for solid tumors, the past century has demonstrated an increased role for multimodality therapy. The goal of

current treatment for solid tumors is to minimize the deformity of wide-scale surgical extirpation, with assistance of neoadjuvant and adjuvant chemoradiation, to provide the greatest likelihood for cure.

Neoadjuvant treatment is the term used to describe either chemotherapy and/or radiation that are administered prior to tumor excision. Neoadjuvant therapy is used to shrink unresectable tumors rendering them resectable, or to decrease the magnitude of the ablation necessary to achieve negative margins.¹ Patients may undergo a complete response with total preoperative tumor eradication, or a partial response to neoadjuvant therapy. The response to neoadjuvant chemotherapy is an important predictor of outcome and can determine which chemotherapy is used postoperatively.² Clinically neoadjuvant therapy is a common part of treatment algorithms for many solid tumors. For example, randomized trials demonstrate lower recurrence rates for T3 and T4 rectal tumors when chemoradiation is delivered preoperatively as compared to postoperatively.³ Furthermore, for distal tumors lying near the anus, neoadjuvant therapy facilitates sphincter preservation by converting cases that potentially require abdominoperineal resection to low anterior resections.⁴

Neoadjuvant chemotherapy has come to play a significant role in the management of breast cancer, with significant impact on reconstructive decision-making for the plastic surgeon. Traditional indications for neoadjuvant chemotherapy include large tumor size, N2 nodal status, and inflammatory component. More recently it has been advocated for tumor down-staging and to facilitate breast conservation.⁵ Increased use of neoadjuvant therapy in breast cancer has resulted in recognition of pathologic complete response, whereas no tumor is identified on surgical specimen following completion of chemotherapy. Further study is required to determine if the need for ablative surgery is obviated in this setting.⁶

Disadvantages of neoadjuvant therapy include the possibility for disease progression prior to surgical resection and increased rates of surgical complications due to side effects of chemoradiotherapy. For example, in a review of nearly 1200

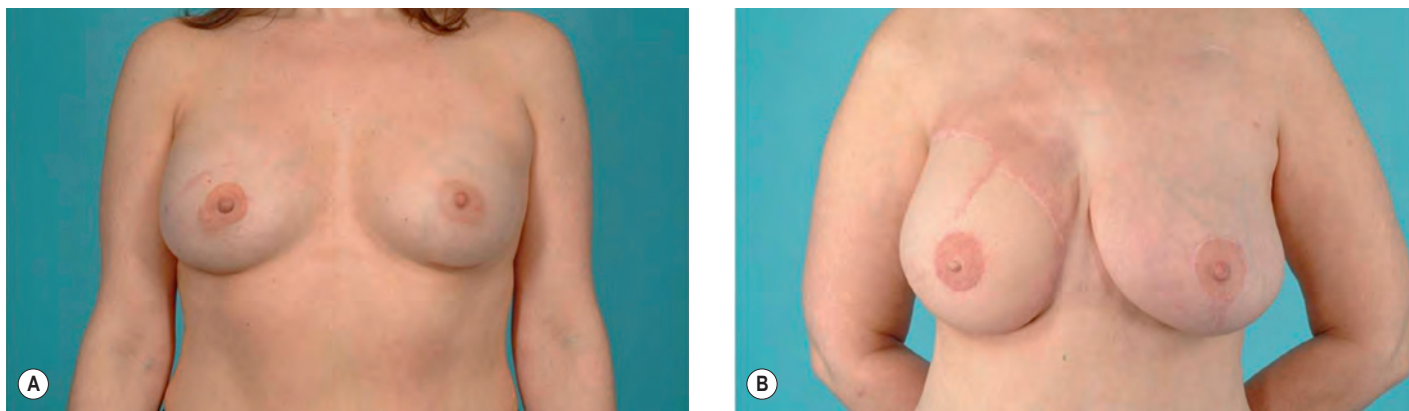


Fig. 11.1 Superiority of lesser resections to radical surgery. **(A)** This patient had a less aggressive surgical approach with a nipple-sparing mastectomy followed by immediate autologous tissue reconstruction. **(B)** The second patient had a more aggressive modified radical mastectomy, followed by radiation and delayed reconstruction. Note that while both patients have acceptably cosmetic reconstruction, the outcome of the patient shown in (B) is inferior to that of the patient shown in (A). In part due to the extensive nature of her surgery, she has more extensive and noticeable scarring, as well as skin color mismatch.

microsurgical breast reconstructions, Mehrara *et al.* demonstrated that neoadjuvant chemotherapy was an independent risk factor for postoperative complications in breast cancer patients undergoing microvascular breast reconstruction resulting in increased rates of wound complications if surgery was performed less than 6 weeks after completion of chemotherapy.⁷

In the adjuvant or postablative setting, chemotherapy or radiation is implemented to decrease locoregional recurrence or systemic disease by treating microscopic tumor deposits or metastases that are not detectable at the time of surgery. It is important to emphasize, however, that even if radiation or chemotherapy is planned postoperatively, all attempts should be made (if surgically feasible) to obtain microscopically negative tumor margins at the time of surgical resection. This concept is based on the fact that negative tumor margins are an important predictor of local or regional metastases in most solid tumors.⁸

Surgery

The earliest treatment for tumors was fulguration using electrocautery, application of toxic materials, or surgical extirpation. Due to the high local recurrence rates seen after tumor excision, surgical management at the turn of the 20th century developed into a “bigger is better” approach with wide margins. The best-known example is the Halsted radical mastectomy for invasive breast cancer advocating the removal of the pectoralis major muscle, all of the breast tissue and axillary nodes.⁹ Similarly, head and neck malignancies were treated with internal jugular vein ligation, sternocleidomastoid muscle resection, and spinal accessory nerve sacrifice. Such aggressive approaches to tumor control have subsequently been shown to be unnecessary for many cancers. Instead, the efficacy of limited anatomic resections has been proven in studies which: (1) demonstrate equivalency with more radical approaches, or (2) combine surgery with multimodality therapy. For example, margins greater than 2 cm have shown no benefit in the treatment of cutaneous melanoma.¹⁰ Additionally, effective treatment of breast cancer no longer mandates mastectomy if lumpectomy is combined with postoperative radiotherapy.¹¹ Nipple areola-sparing mastectomy would have at some time been considered

unthinkable and today is being utilized with ever increasing indications. Modern surgical therapy uses insight gained from clinical trials to minimize the scope of resection with an eye on preserving form and function (Fig. 11.1). Radical approaches are reserved for only the most advanced cancers with extensive local invasion.

While the utility of primary tumor excision has been established, the role of surgery in management of metastatic disease is less clear. The majority of patients with metastasis receive palliative treatment with radiation to achieve local control and chemotherapy for disseminated disease. However, if thorough evaluation reveals isolated or a limited number of metastases in a patient with a good prognosis, both cure and extended survival have been achieved with surgical “metastectomies”. Patients with extremity sarcomas who undergo pulmonary resections have 5-year survival rates up to 25%.¹² Similarly, hepatic lobectomy for colorectal metastasis is associated with 25–40% 5-year survivorship in selected patients.¹³

Finally, surgeons may be called upon to obtain tissue for diagnosis of a new mass. Depending on tumor size, either incisional or excisional biopsies are performed as a precursor to definitive resection or to establish a diagnosis for cancers treated nonsurgically. Incisional biopsies should always be oriented in a direction that facilitates future wide surgical excision.

Radiation

Ionizing radiation is defined as energy sufficient to release electron(s) from an atom or molecule. Most radiation agents use either photons or electrons to cause ionization. The quantity of ionization produced in air by a beam of radiation is termed the exposure and is measured in units of roentgens. The more clinically relevant measure is the absorbed dose, which is a calculation of the amount of energy absorbed per unit mass. This is quantified in joules per kilogram, or gray units (Gy). Upon entering tissues, the ionizing agent dose increases, but then degrades exponentially as its distance from the source increases in accordance with the inverse-square law.¹⁴

The mechanism whereby ionizing radiation achieves tumor cell kill is not completely understood. Ionizing radiation causes cellular damage directly through release of electrons

or indirectly by producing free radicals from water. Since oxygen increases the half-life of reactive radical species, radiation is most effective in oxygen-rich environments. When electrons or free radicals come into contact with biologically important molecules, such as DNA, detrimental effects occur. Although cells efficiently repair single-strand DNA breaks, double-strand breaks are less easily handled by cellular machinery. If sufficient DNA damage accumulates prior to the next mitotic cycle the cell is overwhelmed, leading to cell killing. When the interval between successive doses of radiation is increased, greater numbers of cells can repair DNA strand breaks. This principle is termed sublethal damage and provides the rationale for radiation delivery in fractionated daily doses ranging from 1.8 to 2.5 Gy. The success of radiation therapy is predicated on the fact that normal cells have a greater ability to repair sublethal damage between radiation fractions than tumor cells. Radiation therapy is most commonly delivered at a distance from the tumor called external-beam radiotherapy or teletherapy; however, it can also be administered as brachytherapy with high doses given directly into a specified area.¹⁴

Clinical use of radiation therapy began in the 1940s and 1950s after early pioneers in the field were able to minimize local complications such as radiation burns and secondary skin cancers. Although uncommon, radiation can be used as monotherapy for radiosensitive tumors such as Hodgkin's disease.¹⁵ For other tumor types equivalency between surgical excision and radiation therapy has been demonstrated. For example, treatment of T1/T2 prostate cancer with either radical prostatectomy or external-beam radiotherapy has comparable survivorship, but with different risk profiles for each therapy.^{16,17} Choice of treatment is based on patient preference and surgical risk factors as assessed by the treating urologist. Similarly, aerodigestive tumors of less than 2 cm respond equally well to either radiation or surgery. In the case of laryngeal neoplasms, radiotherapy is preferred due to its ability for preservation.¹⁸

Surgeons most commonly use radiation as part of neoadjuvant or adjuvant regimens in combination with extirpation for solid tumors. These two modalities complement each other to improve locoregional control. While surgery fails at tumor margins where cell counts are low or microscopic, radiation works best at the periphery where oxygenation levels are highest. Radiation is least effective in the avascular center of necrotic tumor masses where oxygen tension is poor.¹⁹

The efficacy of radiation therapy in reducing local recurrence has led to an increase in use of this modality for many cancer types. This increase is amplified by trends towards minimization of surgical extirpation and the use of neoadjuvant chemotherapy with resultant tumor down-staging. The increased role of radiation therapy in cancer management has led to refinements in its delivery. In the past, radiation was administered in the neoadjuvant setting with the goal of rendering microscopic tumor deposits, spilled inadvertently at the time of resection, incapable of cell division. However, technical difficulties and increased complication rates, such as wound breakdown and infection associated with this schedule of radiation, have led to its preferred use in the adjuvant setting for many cancers. Additionally radiation is a known independent risk factor for the development of postsurgical lymphedema as well as secondary skin malignancies.²⁰

Although the increased rates of wound-healing complications following surgery in irradiated tissues have been thought to be related to the harmful effects of radiation on the local blood supply, the exact cause(s) of this increased risk remains unknown.²¹ In fact, studies have suggested that radiation injury causes depletion of local tissue stem cells and that restitution of these cells with stem cell injections can improve tissue healing.²² Interestingly, recent studies have called into question the ability of radiation to improve survival, and as such suggest the need for more nuanced patient selection and risk stratification.²³

Concerns about toxicity and tissue injury after radiation have led to the development of a number of modalities aiming to increase the precision of radiation delivery. **Intensity-modulated radiation therapy (IMRT)** is an example of this approach combining 3D CT scans and computer software to optimize radiation simulation and delivery. During treatment, the intensity of the radiation beam is modulated by computerized X-ray accelerators enabling delivery of radiation to three dimensional tumor shapes thereby minimizing injury to the surrounding regions. For these reasons, IMRT has gained favor in the treatment of prostate, lung, head and neck, and brain lesions. In addition, recent studies have shown that IMRT can decrease cardiac and pulmonary toxicity in left-sided breast cancers. Recent studies have focused on demonstrating survival benefits to IMRT and decreasing long-term complication rates of radiation.²⁴⁻²⁶

Proton beam therapy is a type of radiation therapy in which a beam of protons (rather than electrons) is used to deliver radiation to the tumor bed. Because these particles are bigger than conventional radiation therapy, the delivery of the treatment dose can be more precisely controlled limiting surrounding tissue and exit dose delivery. These radiation delivery treatments are more complex than conventional therapy since a particle accelerator is required to generate the proton beam. The use of different particle sizes enables radiation oncologists to target tumors at different depths delivering the maximum peak of radiation (called Bragg Peak) at a precise point. The use of multiple photons generated from multiple particles (with variable penetration capacity) enables peak radiation delivery to the entire tumor bed.^{27,28}

Brachytherapy is radiation therapy that is delivered internally to the wound bed after tumor extirpation. In some cases, the radiation source can be placed without tumor extirpation or within the tumor itself to increase radiation dose delivery. This approach enables radiation oncologists to place the radiation source in very close approximation to the tumor bed thereby limiting radiation injury to surrounding tissues or external skin. In this manner, radiation therapy can be delivered safely in some cases even in patients who have been previously treated with external beam radiotherapy.^{29,30}

Chemotherapy

The goals of chemotherapy are similar to those of radiation, namely preferentially to kill cancer cells relative to normal tissues while minimizing toxicity. The success of chemotherapy is due to the fact that normal cells have improved ability to repair damaged DNA and survive relative to cancer cells. For chemotherapy to be successful, complete eradication of all tumor cells is essential. Agents that kill 99.99% of 10^9 tumor cells, the approximate number of cells in a 1-cm mass,

allow a tumor burden of 10^5 cells to remain. Since agents are unlikely to kill every tumor cell in a single administration, chemotherapies are delivered in several rounds to achieve maximal cell killing. Administration of chemotherapy in fractions takes advantage of the fact that some agents are effective only in certain stages of the cell cycle (termed kinetic resistance) and minimizes toxicity at each time point by allowing decreased dosing.³¹ Furthermore, combination chemotherapy using agents with different mechanisms of action and toxicities allows maximal tumor killing while minimizing host side effects. Recognition of chemotherapy toxicity has led to modifications such as regional administration, which allows for increased drug doses with reduced systemic side effects. Examples of this application include isolated limb perfusion for patients with melanoma in-transit metastases or hepatic artery infusion pumps for colorectal liver metastasis.^{32,33}

Chemotherapeutic agents such as nitrogen mustard and methotrexate were first introduced in the 1940s with the intention of avoiding surgery altogether. While effectiveness of chemotherapeutics as single-modality treatment for hematologic malignancies such as leukemia and lymphoma has been demonstrated, their efficacy in primary treatment of solid tumors has not been borne out in most cases. Exceptions include chemotherapy for subtypes of testicular cancer and combined chemoradiotherapy such as the Nigro protocol for anal cancer.^{34,35} A common indication for chemotherapy in the management of solid tumors is for palliation of patients with metastatic disease who are ineligible for curative surgery. In such cases, chemotherapy is administered with the intent of prolonging survival and improving quality of life.

Surgeons most frequently encounter chemotherapy as part of neoadjuvant or adjuvant treatment in combination with tumor excision. Examples of tumors commonly treated in this manner include breast, colon, and head and neck cancers. Synergy between surgery and chemotherapy is exemplified in the case of extremity sarcomas. Previously patients with osteosarcomas were treated with amputation; however, the introduction of neoadjuvant chemotherapy has increased rates of limb preservation with equivalent long-term survival.³⁶

Immunotherapy and biologics

Passive and active immunotherapies are newer forms of cancer treatment that use immune mechanisms to kill tumor cells. In passive immunotherapy the host immune system remains quiescent while therapeutic agents are introduced to eradicate tumor cells. The most common application of this treatment is delivery of monoclonal antibodies against specific tumor antigens (Fig. 11.2). Advantages of this approach are the highly specific nature of the therapy that theoretically decreases both side effects and toxicity. A widely used agent is trastuzumab, a monoclonal antibody that binds to the extracellular segment of the HER2/neu receptor, over-expressed in approximately 25% of breast cancers.^{37,38} Biologics such as trastuzumab and pertuzumab are commonly used as components of neoadjuvant regimens.³⁹

Adoptive immunotherapy is an alternative form of passive immunotherapy wherein cells with antitumor activity are introduced into the host (Fig. 11.3). An example would be *ex vivo* manipulation of host autologous tumor-infiltrating lymphocytes, which have a naturally occurring reactivity to

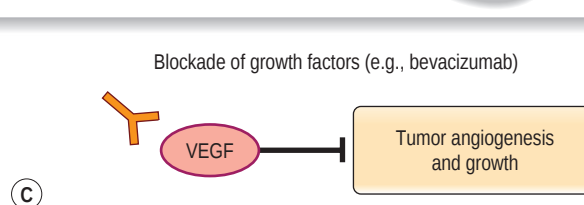
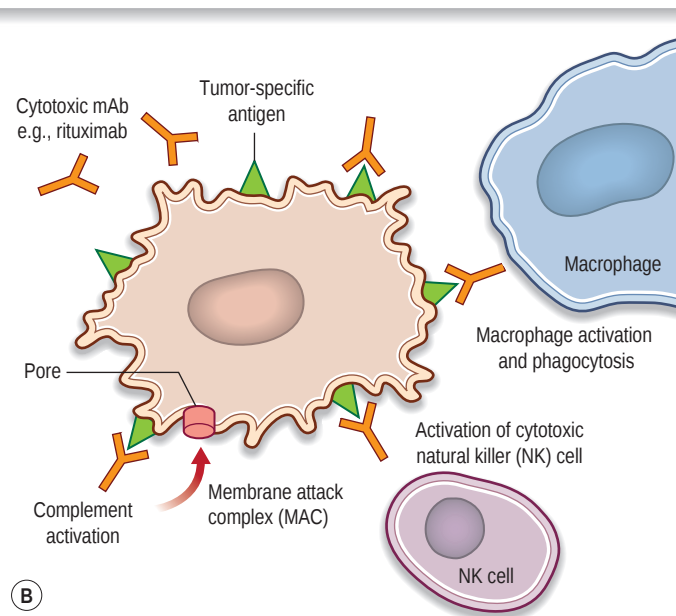
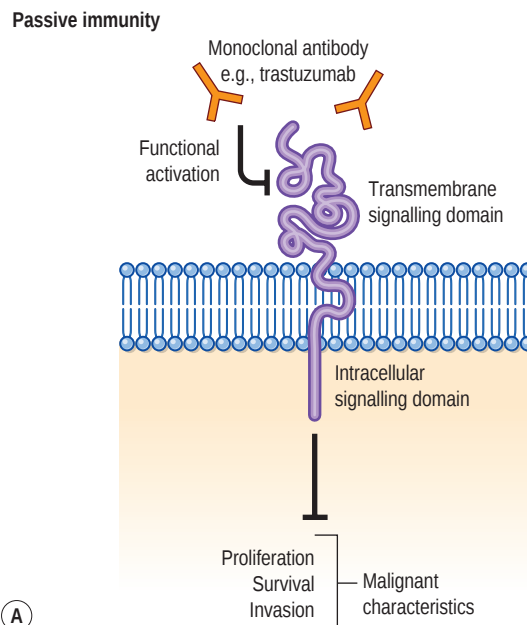


Fig. 11.2 Passive immunotherapy with monoclonal antibodies (mAb). **(A)** Monoclonal antibodies can act by binding a cell surface molecule that acts as a signal transducer. Antibody binding to this molecule inhibits its ability to transduce signals and activate downstream pathways that confer the malignant phenotypes of cell cycle dysregulation, cellular survival, and metastatic potential (e.g., trastuzumab). **(B)** Monoclonal antibodies can contribute to immunotherapy by cytotoxic effects (e.g., rituximab). Antibody binding to tumor-specific antigen can lead to complement fixation and activation, with ultimate formation of the membrane attack complex that punches pores in the tumor cell membrane. Antibody binding may also cause the activation of cytotoxic natural killer cells or phagocytic macrophages. **(C)** Finally, monoclonal antibodies can bind and block the activity of growth factors that are necessary for tumor maintenance. An example of this is bevacizumab, which binds vascular endothelial growth factor (VEGF) and therefore inhibits tumor angiogenesis.

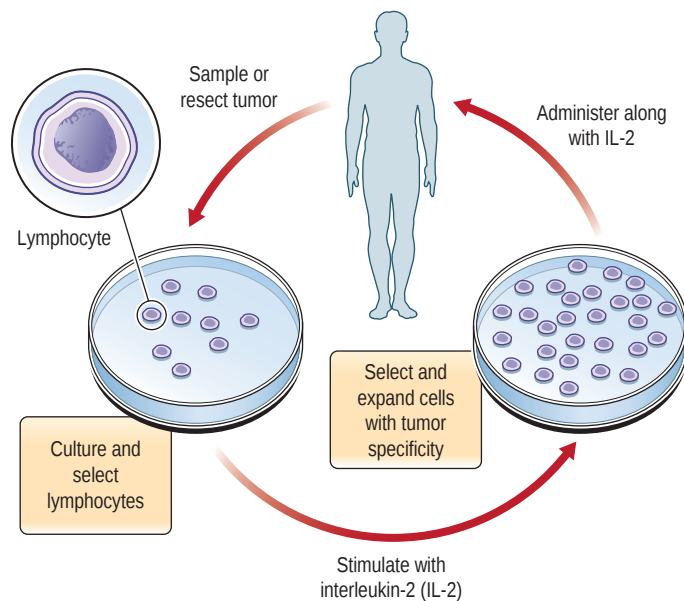


Fig. 11.3 Adoptive transfer of autologous tumor-infiltrating lymphocytes. Lymphocytes are obtained and cultured from tumor specimen. Lymphocyte proliferation is stimulated with interleukin-2 (IL-2). Cells with specificity are isolated and expanded. Patient myeloablation is achieved with chemotherapy and radiation. The expanded antitumor lymphocytes are readministered, often along with IL-2.

cancer, in the presence of IL-2 to increase cytolytic potential or tumor antigen recognition.⁴⁰ Studies are currently evaluating the utility of this therapy for the treatment of melanoma.⁴¹

Active immunotherapy describes protocols in which the host immune system is directly stimulated by presentation of antigenic materials. If the antigenic material causes generalized stimulation of the immune system, it is considered nonspecific stimulation (Fig. 11.4). The best-known immunostimulant agent is bacillus Calmette-Guérin (BCG), an attenuated form of bovine tuberculosis bacillus. Although its mechanism of action is unclear, it has proven benefit in the treatment of superficial bladder cancers, with less promising results as a therapy for melanoma.⁴² Infusions with cytokines are another nonspecific form of active immunotherapy. For example, melanoma is a frequent target for agents such as interleukin-2 and interferon-alpha because it is the tumor with the most immunogenic response.^{43,44}

Agents that elicit a targeted response to either tumor antigens or effector cells are considered specific (Fig. 11.5). The best example of specific active immunotherapy is development of vaccines derived from antigens expressed on patients' cancer cells. The highly specific nature of this therapeutic approach underscores its limitations. For example, multiple patients' tumors may express different peptide antigens or alternatively different subclonal populations may exist within a single individual.

The latest generation of antineoplastic agents, called biologics, targets molecular pathways identified from basic science tumor biology. In contrast to traditional methods, which develop drugs through trial-and-error testing, drug creation in this manner is referred to as rational design since targets are specified *a priori*. Since many biologics are antibodies, they may be considered as forms of passive immunotherapy. The earliest example, imatinib (Gleevec), was designed to block the abnormal gene product of the Philadelphia chromosome,

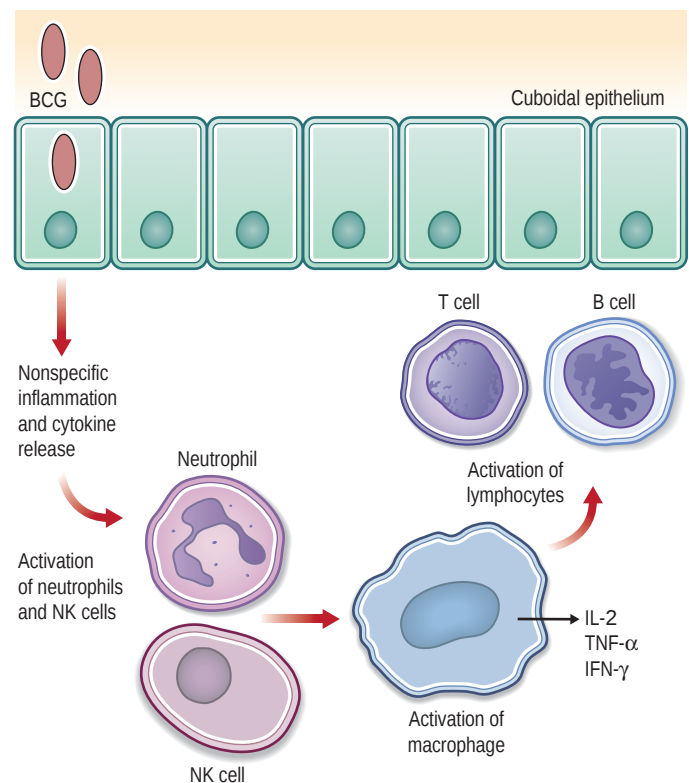


Fig. 11.4 Active immunotherapy with a nonspecific agent such as bacillus Calmette-Guérin (BCG). Administration of the agent causes a nonspecific inflammatory reaction with attendant cytokine release. This results in activation of neutrophils, natural killer (NK) cells, and macrophages. These cells in turn release various cytokines, including interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF-α), and interferon gamma (IFN-γ). These cytokines in turn lead to activation of lymphocytes and resultant tumor cell killing.

the constitutively active Bcr-Abl tyrosine kinase.⁴⁵ Clinical efficacy with imatinib has led to targeting of other oncogenes such as vascular endothelial growth factor with bevacizumab (Avastin) and CD20 with rituximab (Rituxan). As the newest class of antineoplastic agents, the role of biologics in the chemotherapeutic armamentarium is under investigation.

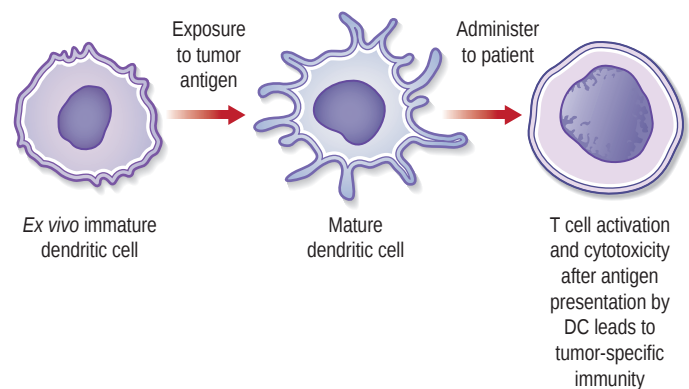


Fig. 11.5 Active immunotherapy with tumor vaccination. A variety of approaches to tumor vaccination have been applied, with variable results. An approach that has been advocated recently utilizes *ex vivo* activation of the antigen-presenting dendritic cell (DC). Immature DCs are expanded *ex vivo*. They are then exposed to a tumor-specific antigen and stimulated. The resultant mature DCs are administered to the patient. These cells act as antigen presenters, leading to activation of T cells with specific antitumor activity.

With widespread availability and use, plastic surgeons will increasingly operate on patients who receive them. Few data are available about surgery in this setting, but case reports suggest angiogenesis inhibitors such as bevacizumab contribute to wound breakdown since neovascularization is a key component of normal wound healing.⁴⁶

Photodynamic therapy

Photoradiation uses light within the visible spectrum to produce energy within cells. The most widely known application of photoradiation is lasers. Chemicals called photosensitizers, which are preferentially taken up by cancer cells relative to normal tissues, respond to light by producing free radicals. When light is shone on these cells, accumulation of energy leads to thermal damage and cell killing.⁴⁷

Since photodynamic therapy requires light to be activated, its utility is limited to superficial tumors. Photodynamic therapy is currently being used for the treatment of advanced esophageal and non-small cell lung tumors and is under investigation for oral, skin, and other cancers.^{48,49}

Pathobiology

Understanding of tumor cell biology provides a foundation for current clinical management of cancers.

Critical mass

Normal cells tend not to overcrowd one another and align themselves in an orderly fashion. In contrast, tumor cells lose this propensity and grow by overlapping each other. Tumor cells grow in a logarithmic fashion, quantified as the doubling time. Each tumor grows at a different rate so doubling times can vary between 2 and 200 days.^{50,51} Tumors are generally not detectable until they reach approximately 1 cm in diameter. Depending upon the doubling time, a tumor may be present in a patient for years before it becomes palpable. Understanding this concept affords the oncologic team sufficient time to evaluate newly diagnosed patients properly and thoroughly without rushing therapy. The first step, when technically feasible, is to obtain a biopsy of a tumor mass to establish the cell type and correct diagnosis. Excisional, incisional, or needle biopsies are performed depending on the size and location of the tumor. In some cases, for example, renal cell cancer, needle biopsy or incisional biopsies may be contraindicated as these procedures can cause peritoneal seeding. Tissue diagnosis is usually correlated with imaging studies such as computed tomography scans or magnetic resonance imaging to identify distant and regional tumor spread. Supplied with this information, informed decisions can be made with the patient about the best treatment and timing of adjunctive therapies relative to surgery.

Tumor margins

Variability in the distribution of tumor cells within a given tissue sample can hamper the identification of malignant cells in tissue sections. For example, if 10% of cells in a specimen have a malignant phenotype they are easily visualized using a microscope. However, if the number of malignant cells decreases to 0.1% or 1 in 1000, unless clustered together,

identification of these cells can be challenging and may require more sensitive measures such as immunohistochemistry (to label tumor antigens). Even these more sensitive measures may miss small foci of cancer metastases, therefore resulting in false negative diagnosis. Accurate diagnosis of surgical margins and biopsy specimens is critical since false negative findings can have a significant effect on diagnosis and treatment.

Clinical findings illustrate this concept. For example, patients with head and neck squamous cell cancers who undergo prophylactic lymphadenectomy have significant rates of local recurrences despite absence of tumor cells on final pathology.⁵² A second example can be seen in rectal cancers with negative margins on initial resection. Evaluation of patients with locally recurrent disease shows that 50% occur at the suture line despite negative histology.⁵³ Tumor recurrence in these scenarios may be attributable to microscopic tumor deposits not detected on pathologic evaluation.

Laboratory studies have also demonstrated the presence of microscopic tumor cells. Examples exist in both head and neck and melanoma specimens where cancer cells cannot be detected in routine histology, but have been successfully grown *in vitro*.^{54,55} More recently, molecular biology techniques such as polymerase chain reaction and immunohistochemistry have been used to perform molecular ultrastaging of histologically node-negative patients for identification of microscopically invisible tumor deposits. Whether such small tumor burdens are clinically significant is the subject of further investigation.⁵⁶

The aforementioned examples provide justification for multimodality treatment of solid tumors managed primarily with surgical extirpation. Although margins are frequently reported as “negative”, recurrences often occur. Chemotherapy or, more commonly, radiation is used in these settings to treat potentially viable occult tumor cells. Alternatively, it should be noted that the immune system has the potential to eradicate residual tumor cells remaining after extirpation. Review of patients with positive margins of basal cell cancer demonstrate recurrence rates of only 20–30%, suggesting the body’s capacity to destroy small numbers of cancerous cells.⁵⁷ Ideally the goal of cancer diagnosis is to identify patients accurately with microscopic spread of tumor to avoid unnecessary delivery of adjuvant agents that have untoward side effects and toxicities.

Classification

Tumor classification can be based on a number of different factors, including morphology, degree of differentiation, and histologic cell type. Classification schemes differ for each tumor type since factors that determine behavior are variable. Retrospective studies have identified tumor characteristics that may be used to predict the clinical behavior of the tumor type. For example, sarcoma behavior correlates with the number of mitoses identified per high-power field or histologic subtype.^{58–60} In contrast, prognosticators for breast cancer include tumor size, lymph node status, and hormone receptor expression.^{61–64} The principal goal of classification schemes is to substratify tumors to predict clinical behavior more accurately and guide therapy. Although recent advances have been made in this field, the quest for more accurate diagnosis and prognostication of tumor behavior is a major source of

current research. In the future, the goal is to identify tumors based on “genetic signatures” that enable not only more accurate diagnosis, but also targeted treatment.

The oldest classification system is based on clinical findings. Here, staging is based on degree of tumor spread, presence of lymph node involvement, and presence of distant metastasis by either radiography or biopsy. The widely used TNM system expounded on clinical classification systems in an attempt to stratify patients further into prognostic groups. In this system, tumor (T) represents the extent of the primary tumor as measured in size, depth of invasion, or degree of anatomic involvement. Node (N) enumerates involvement of lymph nodes, such as the number of affected nodes or node size. Metastasis (M) reflects the involvement of distant organs.

Other classification systems rely on tumor morphology as the basis for prognosis. For example, Lund’s classification for basal cell carcinomas is based upon descriptive features of the tumor such as nodular (well-defined margins), ulcerative, morphea and sclerosing patterns (indistinct margins). In this system, the presence of either morphea or sclerosing features is associated with a more aggressive and problematic course.⁶⁵ A second example is the morphologic classification established by Clark for melanoma, which includes lentigo maligna, superficial spreading, nodular, acral, and desmoplastic variants.⁶⁶

Histologic classification systems use histologic cell type or category to stratify clinical outcomes. Examples of histologic grading systems include salivary gland tumors, which are separated into mucoepidermoid, adenoid cystic, acinic cell, and squamous cell subtypes.⁶⁷ Clark’s histologic system categorized melanomas by level of invasion into the papillary and reticular dermis and subcutaneous fat.⁶⁶ Using this approach, determination of the depth of invasion was subjective with poor interrater reliability. Subsequently, Breslow’s system was developed which more objectively quantitated tumor thickness by measurement with a micrometer attached to the microscope field.⁶⁸

More recently, molecular biology concepts have been applied to tumor classification. Knowledge of the transcriptome and proteasome of tumors has led to identification of unique molecular signatures for each tumor that predict clinical behavior. An example is the reproducible and highly specific molecular signature of the clinically aggressive triple-negative (absent for ER/PR/HER2 receptors) breast tumors.⁶⁹ Through use of basic science techniques, investigators aim to subclassify tumors on a molecular level to refine staging schemes and provide tailored therapy.

Management

The oncologist’s goal is to apply available treatment options, both surgical and nonsurgical, to minimize morbidity while enabling patient cure. In addition, the relative value of reconstruction in restoration of organ function and cosmesis is not equivalent in all scenarios and may play a role in choosing an oncologic regimen. For example, laryngeal cancer treatment with radiotherapy is strongly preferred over laryngectomy since current methods of voice reconstruction are inadequate.

In contrast, many breast cancers are treated equally well with either lumpectomy and radiotherapy or mastectomy alone. These situations require detailed consultation with a

comprehensive oncologic team about the risks and benefits of each therapy with informed decision-making by the patient. Furthermore, the availability of highly effective autologous and implant-based breast reconstruction techniques may further influence the decision to proceed with simple mastectomy. Similarly, limb preservation for osteosarcomas has only become possible through use of neoadjuvant chemotherapy and functional reconstructions with allografts or endoprostheses. These examples highlight a paradigm shift in ablative strategies over the last century from a “Halstead approach” to modern treatment that relies on advances in both multimodality therapy and reconstruction to manage solid tumors.

Beyond primary tumor mass excision, the treatment of draining lymph nodes is an important part of solid tumor management. Since carcinomas drain through regional nodal basins, in contrast to sarcomas that spread hematogenously, removal of regional lymph nodes is crucial for these malignancies. Regional lymphadenectomy is routinely performed as part of staging to determine prognosis and for its potential therapeutic value.^{70–74}

For patients with clinically palpable nodes at the time of tumor resection, removal of involved nodes is generally performed to achieve regional control by preventing mass effect and skin breakdown. In cases with no clinical evidence of lymph node involvement either on examination or radiographically, the timing of lymphadenectomy is controversial. Lymph node dissection can be performed either at the time of initial tumor extirpation, termed prophylactic or elective lymph node dissection (ELND), or when the tumor subsequently recurs in a nodal basin (therapeutic lymph node dissection, or TLND). ELND is not routinely recommended for two reasons. First, regional lymphadenectomy leads to increased morbidity such as extremity lymphedema or complications of surgical dissection such as nerve damage. Second, ELND has not clearly demonstrated improved survival compared to TLND for malignancies such as melanoma.⁷⁵ Ideally, ELND should be restricted to cases with high probability of occult regional tumor spread such as head and neck cancers with a large primary tumor.⁷⁶

The introduction of the sentinel lymph node concept by Morton *et al.* has further altered surgical management of clinically negative regional lymph node basins.⁷⁷ The sentinel node concept is based on the fact that tissues drain into regional nodes in a reproducible and orderly fashion. After injection of either radioactive colloid or blue dye into the tumor, the first or sentinel node draining the basin is excised to be examined for tumor involvement. The status of the sentinel node is representative of the entire regional nodal chain, suggesting whether or not ELND should be performed. Through careful intraoperative identification of the sentinel node and thorough histologic analysis, false negative rates for sentinel node biopsy now range from 0 to 11%.^{78,79} A subset of patients with negative sentinel nodes on hematoxylin and eosin stain will have micrometastatic disease present on immunohistochemistry. The consequence of such small tumor deposits is unclear since these patients have similar survivorship to controls.⁸⁰ An additional benefit of sentinel node mapping is that, since only a single node is harvested, more thorough histologic and pathologic evaluation is performed of the specimen for improved nodal staging accuracy.

Theoretically, sentinel node mapping should decrease the number of unnecessary regional lymphadenectomies performed with associated morbidity. Rates of extremity lymphedema with sentinel node mapping have decreased to 5% compared with 35% for complete lymphadenectomies.^{81,82} Currently sentinel node mapping is performed for breast cancer and melanoma while reliability of the concept in head and neck, lung, and uterine cancers is under investigation.⁸³⁻⁸⁵

A second major issue to consider when performing lymphadenectomy is the extent of dissection. Arguments supporting extended or radical lymphadenectomy are that greater node removal more accurately stages disease and failure to remove these nodes leaves residual cancer cells behind. For example, colon cancer guidelines recommend that at least 12 nodes be evaluated histologically to avoid a false-negative nodal status.⁸⁶ Arguments against routine use of extended lymphadenectomy include increased morbidity of dissection and lack of a survival benefit compared to limited dissections in randomized trials.

A comprehensive discussion of cancer surveillance is beyond the scope of this chapter, though some points are worth mentioning. Although the premise behind surveillance is to improve outcome through early detection, few protocols demonstrate an actual survival benefit. For example, head and neck patients with asymptomatic recurrences identified through screening methods demonstrate no survival difference compared to patients who presented with symptoms.⁸⁷

Concerns have also been raised that reconstruction may obscure recurrence detection, but data do not support this contention. Maxillectomy defects reconstructed with flaps, as opposed to obturators, demonstrate statistically comparable times to recurrence.⁸⁸ Similarly, for breast cancer neither implant nor autologous reconstruction has been associated with a delay in diagnosis of recurrent disease.^{89,90} Recurrences after transverse rectus abdominis myocutaneous flap reconstruction can be successfully managed with local excision and flap salvage in 80% of cases. Regardless of the type of breast reconstruction performed, recurrent disease is detectable on physical exam, not mammography.

Conclusion

Today, the most common treatment for solid tumors remains surgical excision; however, the last century has demonstrated the advantages of multimodality therapy using chemoradiation. Refined staging and increased knowledge of pathobiology have allowed individualized tumor management with development of targeted treatment regimens. It is incumbent upon plastic surgeons to understand the principles of cancer management in order to perform reconstructions that minimize postsurgical complications, thereby allowing patients to receive adjunctive therapy in a timely manner.



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Stem cells and regenerative medicine

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SYNOPSIS

- There exists a significant clinical need for tissue reconstruction and regeneration.
- Stem cells are a key building block to any tissue regeneration or engineering strategy.
- Stem cells can be derived from multiple sources and tissues at various stages of differentiation.
- Stem cells can have different *in vitro* and *in vivo* capabilities and are at different stages in bench and bedside research:
 - embryonic stem cells
 - postnatal and somatic stem cells
 - adipose-derived stromal cells (ASCs)
 - mesenchymal stem cells (MSCs)
 - tissue-specific stem cells
 - induced pluripotent stem (iPS) cells
- Prospective clinical applications for stem cell therapy will likely require multidisciplinary approaches employing tissue engineering and inductive therapies (including biomimetic matrices, gene therapy, small molecules, and growth factors).

- Mesenchymal stem cell differentiation has been elucidated using specific *in vitro* and *in vivo* protocols.
- Adult, or tissue-specific, stem cells are undifferentiated cells that are found in almost all tissues and organs after embryonic development.
- Postnatal stem cells can be reprogrammed into an “embryonic-like” state called induced pluripotent cells.

Discussion of biomedical burden (Fig. 12.1)

As the global population ages and expands, the associated incidence of pathology secondary to congenital, postsurgical, post-traumatic, vascular, and degenerative etiologies (such as arthritis, osteoporosis, chronic wounds, post-oncologic resection) also continues to increase. In 2007 it was estimated that the United States alone spent over 26 billion dollars on treatment for diseases of the musculoskeletal system, with an average annual growth of 8.5% (second highest growth of all body systems).¹ The American Society of Plastic Surgery additionally estimates that almost 5.8 million reconstructive procedures were performed by plastic surgeons in 2014, with over 4.4 million cases performed for tumor removal and cancer reconstruction, and over 102,000 for breast reconstruction.²

Tissue reconstruction remains a significant challenge for plastic surgeons when treating patients suffering from traumatic injury, oncologic extirpations, and congenital anomalies. While synthetic prostheses, plates, and implants to correct soft-tissue defects have greatly improved the lives of millions of patients, such artificial tissues are plagued by suboptimal durability and increased risk of infection. While some of these problems have been mitigated by the use of cadaveric and autogenous grafts, the grafts too are limited by durability, availability, and donor site defects.

Plastic surgeons must thus struggle with the inadequacy of current implants and grafts, and the failure of these therapies to recapitulate the ability of dynamic living tissue to remodel and regenerate in response to environmental cues. To address this, the focus of reconstructive strategies must ultimately shift from simple tissue repair to tissue regeneration. Tissue

Introduction

- Three characteristics that define a stem cell are:
 1. Self-renewal: stem cells can expand and give rise to a clonal population of cells through cell division.
 2. Clonality: stem cells are able to give rise to new stem cells.
 3. Differentiation potential: stem cells can differentiate *in vitro* and *in vivo* into multiple mature cell types and reconstitute a specific tissue type following transplantation.
- Stem cells can come from embryonic or postnatal sources.
- Embryonic stem cells exist in a more primitive pluripotent state than postnatal, somatic, and tissue-specific stem cells.

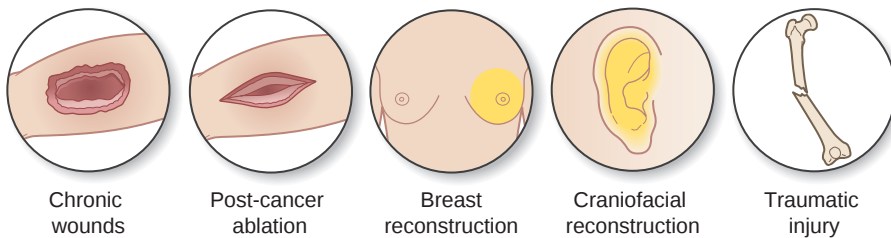


Fig. 12.1 Biomedical burden. Different tissue reconstructive challenges faced by plastic surgeons. From left to right, possible applications of tissue engineering include treatment of chronic wounds, post-cancer ablation, breast reconstruction, craniofacial reconstruction, and traumatic injury.

regeneration, in short, involves the use of a biologically active scaffold, seeded with a pluripotent, self-renewing cell type such as stem cells (Fig. 12.2). The synergy of the biomimetic scaffold with a competent cellular element (e.g. stem cells) will ideally allow the regeneration of tissues in response to injury.

Stem cells are defined functionally as a clonogenic population of cells capable of self-renewal and differentiation into committed progenitors. These progenitors can then differentiate further into mature cell types and form functional tissues.³ Traditionally, stem cells have been divided into two categories based on their differentiation potential: pluripotent stem cells and multipotent stem cells. Pluripotent stem cells (also known as embryonic stem cells) are capable of differentiating into any cell type in the body, whereas multipotent stem cells (also called adult stem cells) are more restricted in their potential and can give rise to multiple, but not all, cell lineages. Recently, in addition to this traditional stem cell classification, a new class of stem cells has been described, called induced pluripotent stem cells (iPS cells). iPS cells are derived from genetically reprogrammed adult cells and are believed to have the same differentiation potential as embryonic stem cells.

Why stem cells and regenerative medicine should be of interest to plastic surgeons

Plastic surgeons are optimally positioned to utilize adult stem cell populations in clinic as they have direct access to a plentiful supply of adult stem cells. Specifically, plastic surgeons can obtain large quantities of adipose tissue from liposuction and body-contouring procedures. From this tissue, adipose-derived stromal cells may be extracted for therapeutic use.

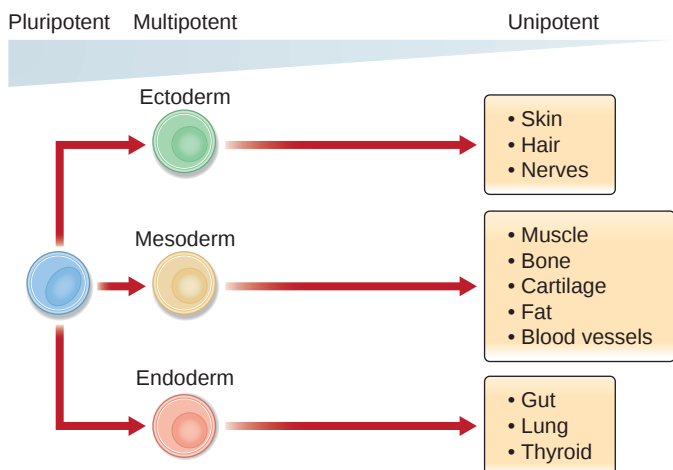


Fig. 12.2 Differentiation of pluripotent stem cells down different multipotent lineages. An embryonic stem cell is a pluripotent stem cell, whereas an adipose-derived mesenchymal cell is a mesodermal multipotent stem cell.

Ideally, fully developed stem cell technology would enable the utilization of prefabricated biomimetic scaffolds seeded with these cells to address a wide range of soft tissue, skeletal, muscle, cartilage, vascular, or joint defects. Recent studies have shown that there may be differences in the osteogenic and adipogenic potential of adipose-derived stromal cells based on the subcutaneous region from which the cells are harvested. Therefore, surgeons in the future may tailor the region from which they harvest the therapeutic cells to patient-specific needs.⁴

In addition, the potential for clinical utilization of human stem and stromal cells is widely acknowledged and has prompted some individuals to store their own tissues for possible future use. One example of this is the banking of umbilical cord-derived blood.⁵ Similarly, various other adult stem cell types can be frozen for long-term storage.



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Human embryonic stem cells

Definitions

Research in hESCs is a rapidly developing field and has attracted increasing attention over the last fifteen years. The ability of hESCs to produce any cell type found in the human body has yielded many encouraging new avenues of investigation. Furthermore, hESC research promises to provide a deeper understanding of cellular biology while generating new treatment modalities for many diseases.^{37,38} In addition, the ability of stem cells to repair and regenerate tissue hints at the possible restoration of organ damage once thought to be permanent and return of function once considered irreversibly lost. Despite recent controversy surrounding political and ethical concerns over the research and clinical use of these cells, hESCs continue to be a promising cell source in the field of regenerative medicine.

The term “embryonic stem cell” was coined by Gail Martin to distinguish them from previously described pluripotent embryonal carcinoma (EC) cells derived from teratocarcinomas.²⁹ ESCs possess three essential characteristics: (1) derivation from a pre-implantation or peri-implantation embryo; (2) the capacity to self-renew and proliferate in a prolonged undifferentiated state; and (3) the ability to form derivatives of all three embryonic germ layers.³⁹

As an extension of early work on ESCs in mice, hESCs were first isolated in 1998.³⁹ Donated fresh cleavage-stage human

Historical perspective

Current understanding of clonal stem cell populations has only been validated within the last 40 years. Prior to the 1960s all dividing cells were thought to contribute to tissue growth and turnover, and were generally classified as resident stem cells.³ However, a revolutionizing publication in 1961 redefined existing perceptions of stem cells by isolating a specific population of self-renewing cells in the bone marrow.⁶ This particular stem cell population was discovered by infusing a lethally irradiated mouse with bone marrow cells capable of migrating to the spleen and giving rise to hematopoietic cell nodules. The cells from the nodules were then proven to have been derived from a single cell. Cells capable of giving rise to clonal populations were named “colony-forming units” and eventually shown to be short-term hematopoietic cells. Studies such as this provided the framework for our current understanding of the undifferentiated self-renewing cell population.

The presence of mesenchymal stem cells, a type of adult stem cell, in the bone marrow was first suggested in the late 19th century by Cohnheim, who proposed that fibroblasts involved in peripheral wound healing were derived from the marrow compartment.⁷ In the 1970s, Friedenstein *et al.* demonstrated the existence of “fibroblastoid” cells within guinea pig bone marrow by flushing out cells onto plastic culture dishes and discarding the non-adherent cells.⁸ The remaining spindle-like cells were heterogeneous in appearance but appeared to be capable of forming colonies *in vitro*, giving rise to the term colony-forming unit fibroblasts.^{8,9} When these cells were subsequently transplanted into subcutaneous pockets, they successfully formed heterotopic bone tissue.⁸ Using similar methods, Castro-Malaspina *et al.* effectively isolated colony-forming unit fibroblasts from human bone marrow.¹⁰ Since these early studies, subsequent investigations have shown that these cells could be cultured *in vitro* and differentiated into several cell types within the mesenchymal lineage.^{11,12} What Friedenstein isolated would later be aptly renamed by Caplan to “mesenchymal stem cells.”¹¹

The fundamental characterization of MSCs as a truly multipotent population of cells is attributed to work by Pittenger and colleagues in 1999.¹³ Prior to this report, scientists were unsure whether bone marrow MSCs represented a heterogeneous mixture of committed progenitor cells, each with restricted potential, or individual cells capable of differentiating into fat, cartilage, bone, and muscle. Running human bone marrow aspirates from the iliac crest of over 350 donors through a density gradient isolation procedure resulted in a phenotypically homogeneous population of adherent cells. Flow cytometry analysis confirmed that over 98% of these adherent cells shared the same surface marker profile. Single cells were isolated from this population and re-expanded. These new descendant cells were shown to retain the ability to differentiate into adipocytes, chondrocytes, and osteoblasts.¹³ MSCs thus proven to have the ability to proliferate extensively while maintaining their multipotent nature were identified as true stem cells.

Historically, adipose tissues were presumed to function solely as a metabolic reserve responsible for processing, storing, and liberating high-energy materials in the form of cholesterol and triglycerides. However, scientists in the early 1960s described a stromovascular fraction (SVF) within adipose

tissue that contained fibroblastic-like cells.¹⁴ Subsequent research into this SVF cell type led scientists to believe that they represented an adipose progenitor cell with differentiation potential limited to adipose tissue.¹⁵ But in 2001, Zuk *et al.* demonstrated the ability of these SVF cells to undergo not only adipogenic but also chondrogenic, myogenic, and osteogenic differentiation.¹⁶ The cells were eventually renamed adipose-derived stromal cells or ASCs. Similar to MSCs, ASCs have since been shown to be capable of differentiating into cardiac cells and even neural progenitor cells *in vitro*.^{16–18} Additional investigation has revealed the differentiation potential of ASCs to be much greater than what was initially thought possible.^{18–24}

Cell surface markers on ASCs are similar to those of MSCs; both express CD105, STRO-1, CD29, CD144, and CD166.^{24,25} Due to the abundance and ease of isolation of ASCs in comparison to other adult stem cell populations, investigators have increasingly focused on the potential applications for ASCs in regenerative medicine. For example, numerous studies have demonstrated the regenerative potential of ASCs when seeded onto a polyglycolic scaffold to create an osteoid-like material.^{26–28}

Establishment of embryonic stem cells was first reported in 1981 using pre-implantation mouse embryos.²⁹ Cells from blastocysts were explanted into tissue culture and developed into four individual cell lines. When these cell lines were transplanted into syngeneic murine hosts, they formed well-differentiated teratocarcinomas, suggestive of pluripotent capacity.³⁰ However, early research using human embryonic stem cells (hESCs) was complicated by contentious political and ethical debate surrounding use of human embryos. Until recently, the creation of hESCs necessitated destruction of a human embryo, which inevitably raised various value-of-life objections. Many of these embryos, however, had already been destined for destruction as they were created for the purpose of *in vitro* fertilization, but had been stored long past their viable shelf-life.³¹

In 2009, President Obama expanded federal research funding beyond what had been previously authorized to include more than 100 existing cell lines, in addition to newly created hESCs sponsored by private or state-level funding.³² Under this new provision, federal funds cannot be awarded towards the creation of new stem cell lines if the creation involves the destruction of an embryo. In response to this restriction, scientists developed a novel method of hESC derivation that does not necessitate damage to the embryo.³³ Using a single cell biopsy technique similar to that used for pre-implantation genetic diagnosis, researchers were able to generate two new pluripotent cell lines without damaging the original embryo.³³ This approach additionally allows for potential generation of matched tissue for children born through *in vitro* fertilization.

An important concept in adult stem cell function is that of the stem cell niche, first proposed by Schofield in 1978.³⁴ A stem cell niche describes the microenvironment in which adult stem cells reside and includes signaling pathways and intracellular communications that permit adult stem cells to maintain their function as regenerative cells.³⁵ This structural unit is modulated by surrounding stimuli to sustain adult stem cell populations while also ensuring that they are appropriately activated. Studies in hair follicle, intestinal lining, and bone marrow have provided significant insight into the precise spatiotemporal regulation of this niche.³⁶

embryos produced by *in vitro* fertilization were obtained by Thomson *et al.* and cultured to the blastocyst stage, typically 4–5 days post-fertilization. From the inner cell mass (which ultimately forms the embryo), five separate hESC lines were established and successfully maintained in culture for 6 months in an undifferentiated state. All five lines retained the capacity to form teratomas after injection into immunodeficient mice. Histological examination of these teratomas revealed gut epithelium, cartilage, bone, smooth muscle, neural epithelium, ganglia, and stratified squamous epithelium. Similar findings were also described by Reubinoff and colleagues, who derived two additional hESC cell lines and demonstrated expression of the transcription factor Oct-4 in these cells. Oct-4 had previously been shown to be essential for the maintenance of pluripotential capacity in mouse ESCs.^{40,41}

The development of hESCs galvanized research into human embryogenesis, development of birth defects, and cellular mechanisms of a variety of pathologic states. In theory, hESC can be used to treat a wide variety of genetic diseases, cancers, diabetes, neurologic degenerative conditions, and spinal cord injuries. Actual translation into clinical use, however, has been hampered by problems with graft-versus-host disease. One potential solution to this involves the development of several hESC cell lines from variegated genetic backgrounds for tailored use in patients to minimize risk of rejection. Other strategies that have been proposed include the use of autologous donor adult stem cells or the more recently discovered iPS cell.^{13,17,42}

Concerns regarding xenogeneic contamination of stem cells during culture have also been raised. hESCs are traditionally cultured *in vitro* using mouse embryonic fibroblast (MEF) feeder layers.³⁹ Without MEF feeder layers, hESCs undergo rapid differentiation and lose pluripotency. A feeder-free culture system has been presented by Xu and colleagues employing Matrigel in medium conditioned by MEFs. However, even with this system, hESCs are still exposed to murine products in order to maintain pluripotency.⁴³ Fears of xenogeneic contamination were further substantiated in 2005, when Martin *et al.* reported the presence of a nonhuman sialic acid Neu5Gc on the cell surface of hESCs.⁴⁴ As humans are unable to generate this particular sialic acid, this finding likely represented uptake from media containing animal products and incorporation through glycosylation. When these hESCs and their derived embryoid bodies were exposed to human serum, rapid binding of immunoglobulin and deposition of complement occurred, ultimately resulting in cellular death.

Circumventing this problem necessitated the creation of a new stem cell line under murine-free conditions. To accomplish this, novel extracellular matrix-coated plates were developed from MEFs and sterilized prior to use.⁴⁵ When hESCs were cultured using these plates, undifferentiated proliferation was observed for 6 months and cells maintained the capacity to form all three embryonic germ layers. This system thus eliminated exposure of hESCs to potential contamination from serum and/or live feeder cells and minimized the risk of disease transmission through contact of cells with animal or human pathogenic agents.

Current concepts and research

Studies utilizing hESCs continue to dramatically revamp our contemporary understanding and treatment of disease

(Fig. 12.3). For instance, technologies developed from stem cell research can be used to manage spinal cord injuries, degenerative neurologic conditions, as well as a variety of genetic diseases. While stem cell investigators have also made significant strides in the fields of diabetes, cardiac, and hematopoietic/vascular research, treatment of spinal cord trauma and Parkinson's disease has recently received more high-profile attention.

The ability for ESCs to undergo neuronal differentiation was first demonstrated by Bain and colleagues in 1995.⁴⁶ After exposing mouse ESCs to retinoic acid, multiple cellular phenotypes were observed, a large percentage of which produced neuron-like outgrowths. Gene expression analysis of these cells revealed several neural-associated transcripts including neurofilaments, glutamate receptor subunits, and nerve-specific transcription factors. Furthermore, physiologic studies demonstrated that these neuron-like cells could generate action potentials. Paralleling these experiments, Schuldiner *et al.* induced neuronal differentiation from hESCs using both retinoic acid and nerve growth factor (NGF).⁴⁷ These neural progenitors were found to be capable of differentiation *in vitro* into astrocytes, oligodendrocytes, and mature neurons.^{40,48} When transplanted into the ventricles of newborn mouse brains, the hESC-derived neuronal cells distributed widely throughout the brain and integrated in a region-specific manner. These findings illustrated the ability of hESCs to respond to local environmental cues *in vivo* to differentiate into appropriate neural lineages. While only preliminary, the results underscore the potential of hESCs to provide novel therapies for the treatment of currently intractable neurological diseases.

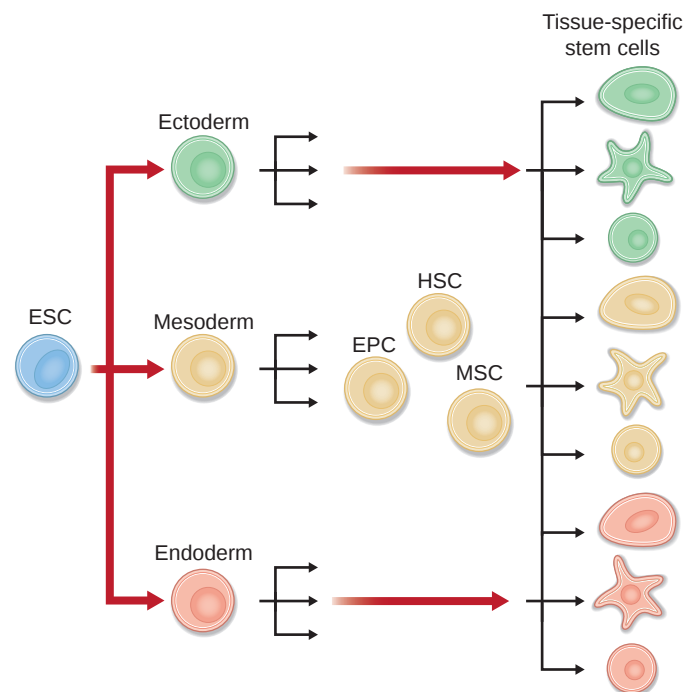


Fig. 12.3 Use of embryonic stem cells. Embryonic stem cells can be used to study genetic changes, screen drugs and design novel therapies. EPC, endothelial precursor cell; ESC, embryonic stem cell; HSC, hematopoietic stem cell; MSC, mesenchymal stem cell.

hESCs have likewise shown promise in the field of diabetes research. At present, the only therapy that is potentially curative for type 1 diabetes is pancreatic islet cell replacement.⁴⁹ Unfortunately, donor shortage has severely limited this modality from becoming a widespread therapeutic solution. Furthermore, the risk of potential disease transmission and cellular rejection also place severe limitations on this treatment modality. The generation of glucose-sensitive insulin-secreting cells from mouse ESCs, however, has introduced a new potential source of cells for treatment of type 1 diabetes.⁴⁹ Culturing hESCs in suspension and allowing for embryoid body formation led to the detection of insulin-producing cells after 14 days of differentiation.⁵⁰ Immunohistochemical staining suggests that 1–3% of the cells are positive for insulin. More recent studies have cast some doubt on these numbers however, estimating their true incidence to be less than 1 per 100 000 cells.⁵¹ While further research is necessary, these studies nonetheless demonstrate the potential to derive cells capable of β -islet function and insulin release that could theoretically be used to replace lost pancreatic cells in patients with type 1 diabetes.

The study of cardiac tissue development has long been handicapped by the lack of a suitable *in vitro* model. The advent of hESC research, however, has also offered a potential avenue for progress to be made in this area. Kehat and colleagues first noted the presence of spontaneously contracting areas within hESCs cultured in suspension and plated to form embryoid bodies.⁵² Cells from these regions, which made up approximately 8% of the entire area, stained positively for a variety of cardiac markers, including myosin, desmin, troponin I, and atrial natriuretic factor. In addition, both positive and negative chronotropic effects were observed in the contracting cells following application of isoproterenol and carbamylcholine. Differentiation of hESCs into these cells was found to be enhanced by the application of 5-aza-2'-deoxycytidine and purified through density centrifugation to obtain a population of cells comprised of 70% cardiomyocyte progenitors.⁵³ In 2003, Mummery *et al.* provided the first demonstration of hESC cardiomyocyte differentiation through co-culture techniques with visceral endoderm-like cells.⁵⁴ This approach mitigated the need for spontaneous cardiogenesis and efficiently produced solid aggregates of beating cells consisting of 10–200 cardiomyocytes. Interestingly, these colonies could be frozen and were observed to resume beating upon thawing. Collectively, the findings strongly argue for the continued development of hESCs as a model for cardiac research. hESC ability to differentiate into cardiomyocytes *in vitro* and the development of technology to enrich these cells represent important initial steps towards the future clinical utilization of hESCs in heart disease.

Investigators have also developed procedures to induce the formation of vascular endothelial cells from hESCs. Endothelial cells play a critical role in repair and regeneration, and investigation into potential use of hESC-derived vascular cells in the treatment of vascular disease is highly clinically relevant.⁵⁵ Zambidis *et al.* first described the presence of mesodermal-hematoendothelial cluster colonies within embryoid bodies at days 6–9.⁵⁶ These colonies were found to consist of non-adherent cells expressing CD45, and gave rise to hematopoietic lineages, as well as adherent cells that expressed markers characteristic for vascular endothelium.

The hESC-derived endothelial cells were then isolated using fluorescence-activated cell sorting (FACS) for CD31 positive cells.⁵⁷ After expansion in culture, the cells were injected into immunocompromised mice and found to form microvascular networks. While their long-term stability is unknown, these derived endothelial cells represent the first step towards potential treatment of vascular disease and stimulation of ischemic tissue growth using hESCs. They also provide a foundation for future study of biomolecular mechanisms involved in blood vessel formation.

Clinical correlates

Clinical use of hESCs remains in its early infancy. The obstacles that must be overcome prior to wide clinical utilization include: risk of tumorigenicity, immunocompatibility, and successful isolation of a pure population of desired cell types for therapeutic use. Nonetheless, work continues on one of the most promising applications of hESCs: neuroregeneration. Preliminary work performed in the murine model has shown potential, leading to the first Food and Drug Administration (FDA)-approved clinical trial incorporating hESCs.

The capacity for regeneration of the central nervous system is limited, making the possibility of repair and return of function through utilization of hESCs particularly compelling. Following trauma, injuries to the brain and spinal cord can result in demyelination secondary to death of local oligodendrocytes.⁵⁸ While axons may be spared, action potential propagation nonetheless can become disrupted, resulting in irreversible loss of motor function. hESCs that have been differentiated into oligodendrocytes, however, can potentially be used to replace lost oligodendrocytes. As a proof of this concept, Keirstead and colleagues evaluated the ability for hESCs to incorporate, re-myelinate, and restore locomotion after spinal cord injury in rats.⁵⁹ In this study, spinal cord contusion injuries were induced in Sprague-Dawley rats at the T10 level using a controlled, reproducible force generator capable of delivering a sudden desired impact. Oligodendrocytes derived from hESCs were purified and delivered both above and below the place of contusion 7 days following injury through direct injection into the spinal cord. Histological analysis 8 weeks later revealed significantly greater density of re-myelinated axons when compared to control animals. More importantly, however, animals that received hESC-derived oligodendrocytes demonstrated significantly higher locomotor function scores, which continued to improve up to 1 month after the initial injury. These findings suggest that transplantation of hESC-derived oligodendrocytes may be an effective means of treating acute spinal cord injuries. Of note, no teratomas were observed in this study, suggesting pre-differentiation of hESCs prior to clinical use may obviate concerns surrounding risk of tumorigenesis.⁶⁰

The oligodendrocyte progenitor cell (OPC), a neural progenitor derived from human embryonic stem cells, has been identified as another promising cell population that could be utilized for clinical CNS regeneration. OPCs have the potential to commit to an oligodendroglial lineage and have been found in a number of animal studies to reduce loss of function following spinal cord injuries.^{61, 62} In 2015, Asterias Biotherapeutics announced the initiation of patient recruitment for a phase I/IIa clinical trial to test the safety and efficacy of OPCs in

individuals with complete cervical spinal cord injury (SCI). The trial is a continuation of the California Institute for Regenerative Medicine (CIRM)-funded clinical trial begun by biotechnology firm Geron in 2010 using the same kind of stem cell to treat thoracic SCI. None of the five patients from the initial Geron trial developed adverse effects such as tumors or inflammation from the therapy, and MRI scans performed throughout the follow-up period found decrease in the size of injury site and suggested that OPCs may have had some positive effect in preventing further spinal deterioration in four out of five patients. Despite these findings, the Geron trial was discontinued due to a reported change in business strategy within the company.⁶³ While it remains to be seen whether positive findings from rat studies can be clinically replicated, this represents an important first step towards the implementation of translational therapies using stem cells to treat human disease. Though full restoration of function following complete paralysis is not expected at this present time, there is hope that patients with less severe injuries may one day benefit from use of hESCs.⁶⁴

Postnatal and somatic stem cells

Adipose-derived stromal cells

Definitions and harvest

Adipose tissue contains a stromal population composed of three main types of cells: microvascular endothelial cells, smooth muscle cells, and multipotent cells. ASCs have the capacity to differentiate into adipocytes, osteoblasts, and chondroblasts *in vitro*.^{16,17,19,65,66} However, the origin of hASCs has not been clearly defined. Several laboratories have hypothesized that these cells represent pericytes surrounding blood vessels, which may explain their ability to differentiate into endothelial cells; others suspect they are a subpopulation of fibroblasts that reside within adipose tissue (Fig. 12.4).

ASCs, like stem cells from the bone marrow, have extensive proliferative potential and can self-renew, as well as undergo osteogenic, chondrogenic, myogenic, and adipogenic differentiation. This population can also be defined by its cell surface markers. ASCs have been shown to be positive for the following cell surface markers: CD105, STRO-1, CD29, CD144, and CD166. They have been shown to be negative for the following cell surface markers: CD3, CD4, CD11c, CD14, CD15, CD16, CD19, CD31, CD33, CD38, CD56, CD62p, CD104, and CD144.^{24,25}

ASC harvest

Human ASC harvest can be performed on human lipoaspirate or resected adipose tissue (Fig. 12.5). Lipoaspiration removes the necessity for mincing adipose tissue, and ASCs have been shown to retain differentiation potential even following ultrasonic-assisted liposuction.⁶⁷ If fat has been harvested from multiple anatomic locations, these specimens should be labeled accordingly and kept separate as material differences exist in the differentiation capacity of adipose cells mined from different subcutaneous depots (Fig. 12.6).⁴

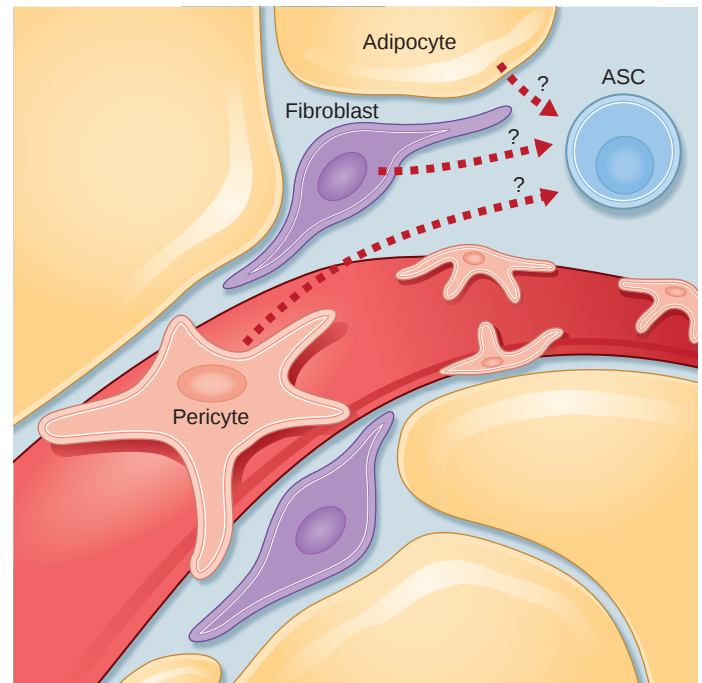


Fig. 12.4 Unknown origin of human adipose-derived stromal cell (hASC). Adipose-derived stromal cells are thought to be derived from adipocytes or fibroblasts or from perivascular mural cells known as pericytes.

Following harvest, the adipose tissue should be processed in a sterile cell culture environment as soon as possible (Fig. 12.7). Adipose specimens should first be washed in dilute Betadine, followed by two phosphate-buffered saline (PBS) washes of equal volume. The tissue should then be digested with an equal volume of 0.075% (w/v) type II collagenase in Hank's balanced salt solution at 37°C in a water bath with agitation at 140 rpm for 60 minutes. Every 15 minutes during digestion, the fat should be agitated and vented. Next, the collagenase digest should be inactivated by adding an equal volume of PBS with 10% fetal bovine serum (FBS) and 1%



Fig. 12.5 Human liposuction of thigh.

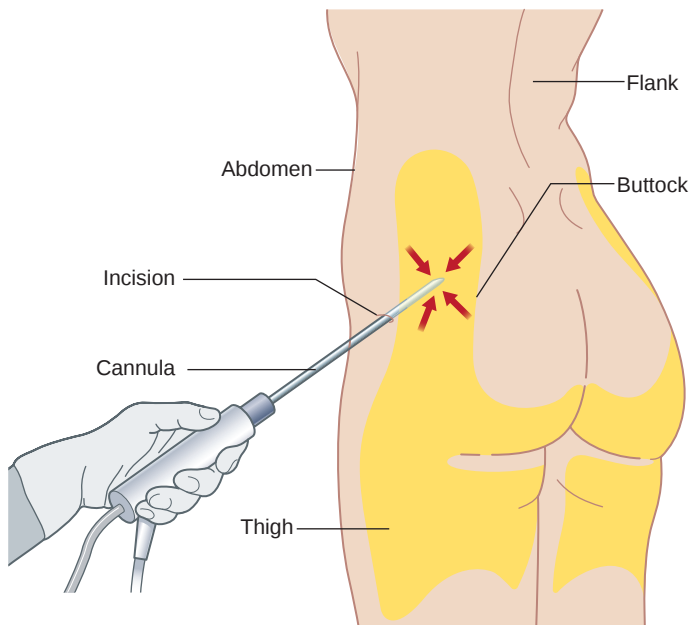


Fig. 12.6 Different locations from which liposuction fat can be harvested. These locations have been shown to demonstrate different osteogenic and adipogenic potentials.

penicillin/streptomycin. The stromal vascular fraction is then pelleted via centrifugation at 1000 rpm for 6 minutes. The supernatant is discarded and the cell pellet resuspended and filtered through a 100- μ m cell strainer to remove undigested tissue fragments. The cells are pelleted and resuspended in growth media, and primary culture is established in tissue culture plates incubated at 37°C in an atmosphere of 5% CO₂. Cell counting can be challenging given the large number of erythrocytes in the final cell pellet. However, we do not recommend a red cell lysis step as we believe this decreases the viability of the ASCs. On average, 10 mL of starting adipose tissue will allow the harvest of 1 million hASCs.

Mouse ASC (mASC) harvests are done in a similar manner. The first step involves harvesting the inguinal fat pad bilaterally from at least four mice. Here, it is imperative to mince the adipose tissue finely prior to the digestion step. Subsequently, the steps are the same as described above for hASCs: a

digestion step, followed by neutralization, centrifugation, filtration, and plating.

Current concepts and research

Difference between mouse and human ASCs

The study of mASCs is attractive due to the relative ease of cell harvest and the availability of laboratory mice. However, important differences exist between mouse and human ASCs. For example, hASCs have been observed to have a significantly more robust *in vitro* osteogenic capacity when compared to mASCs.^{68,69} In order to undergo significant *in vitro* osteogenesis, mASCs require an additional osteogenic stimulus such as retinoic acid.⁷⁰ Moreover, cytokines such as fibroblast growth factor (FGF)-2 abolish osteogenic differentiation in mASCs, whereas hASC osteogenic differentiation proceeds relatively uninhibited both in the presence and absence of FGF-2.^{69,71}

In our laboratory, we observed that ASCs, whether derived from mouse or human origin, contribute to osseous healing of mouse cranial defects.^{72,73} For example, a critical-sized mouse calvarial defect shows no healing without ASC engraftment even up to 16 weeks post-injury. Upon hASC engraftment, however, significant bony healing is observed in as little as 4 weeks post-injury.⁷³

Enrichment based on cell surface receptors

While substantial progress has been made in the study of ASCs, further progress is hampered by the heterogeneity of the cell population. We believe that a select subpopulation of cells with robust ability to differentiate along an osteogenic lineage can be further purified from the current ASC population (Fig. 12.8). Selecting for this enriched subpopulation of ASCs can help maximize outcomes of cell-based therapies in skeletal regeneration. Borrowing from an approach used to isolate hematopoietic stem cells (HSCs), the ASC subset can similarly be enriched based on cell surface markers using FACS. However, heterogeneity may persist even within a specific subset of sorted ASCs. While stem cell populations are known to be heterogeneous, the functional consequences of this heterogeneity have not been fully elucidated. The problem of undefined heterogeneity within stem cells must be overcome before they can be used effectively for therapeutic

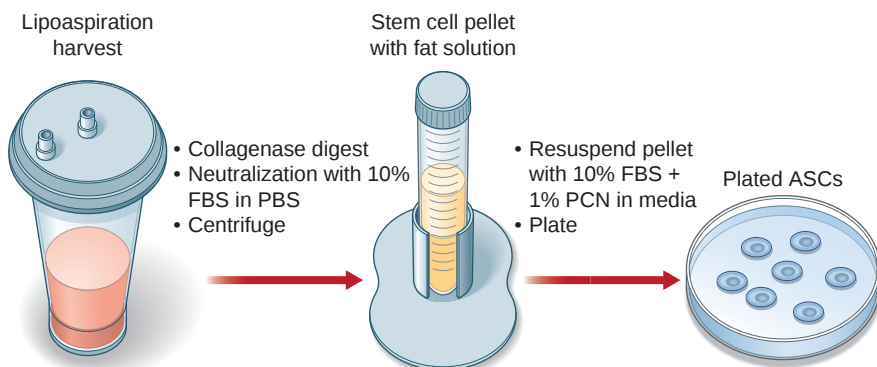


Fig. 12.7 Overview of adipose-derived stromal cell harvest process. Liposuction aspirate (left) is digested, and then centrifuged to pellet the stromal vascular fraction (middle), and then plated in 10 cm dishes for expansion (right). ASCs, adipose-derived stromal cells; FBS, fetal bovine serum; PBS, phosphate-buffered saline; PCN, penicillin.

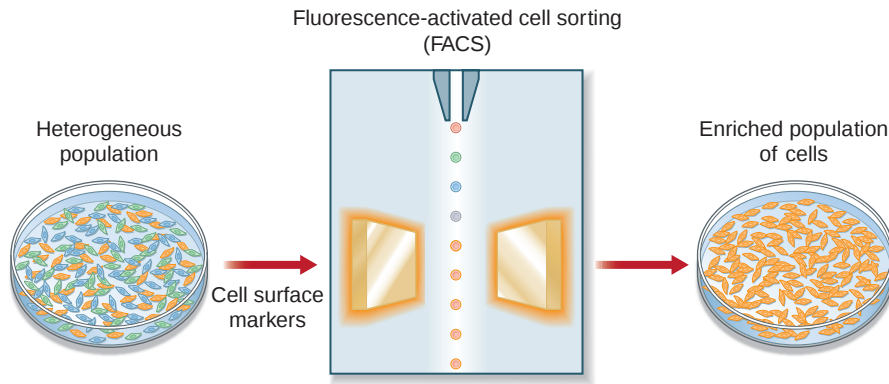


Fig. 12.8 Fluorescence-activated cell sorting (FACS) can be used to separate cells based on cell surface receptors. The goal would be to use these surface receptors to identify cells that are more likely to differentiate down a specific lineage. Here, FACS is used on a heterogeneous human adipose-derived stromal cell (ASC) population to isolate an osteoprogenitor population.

applications. The first step towards understanding this heterogeneity is to elucidate the gene expression profiles of these complex cells. This can be accomplished through single cell microfluidic technology (Fig. 12.9), which permits precise mixing of nanoliter quantities of quantitative PCR reagents to perform transcriptional analysis across individual cells.

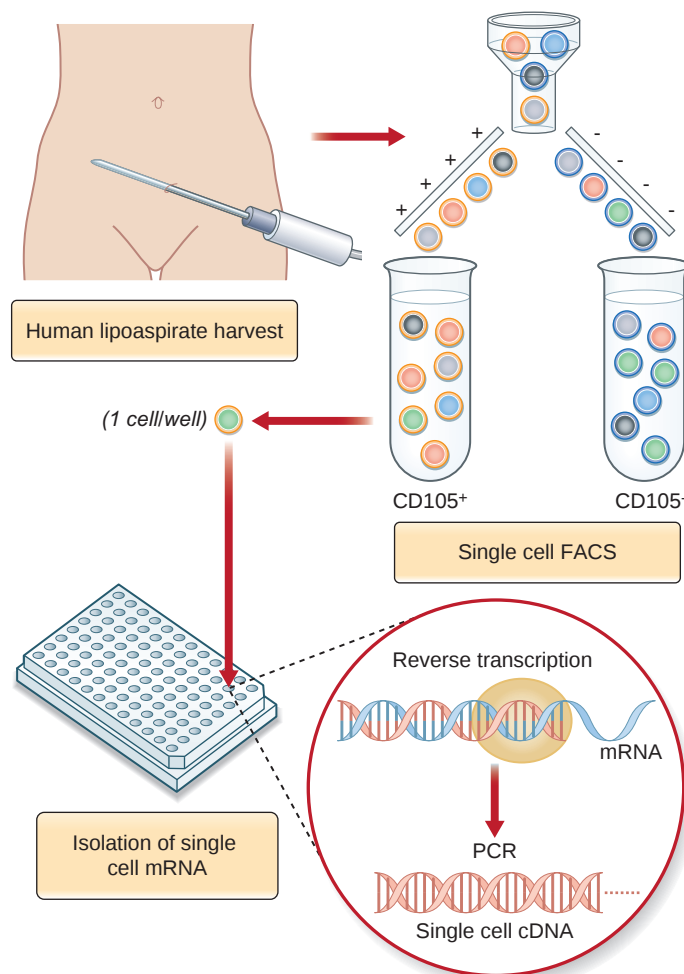


Fig. 12.9 Fluorescence-activated cell sorting (FACS) can be used to isolate cells on a single cell level. Subsequently, human adipose-derived stromal cells can be studied on a single cell level to delineate further the transcriptional properties of each cell. PCR, polymerase chain reaction.

Methods of ASC delivery

Much remains unknown regarding the optimum method for delivering ASC therapy. A significant and growing number of studies have examined the intravenous (IV) administration of ASCs. Such studies have investigated the natural distribution of ASCs following IV injection. Interestingly, most organs show uptake of ASCs after administration, including bone and bone marrow tissues with some studies also showing long-term persistence within the host without oncogenic transformation.^{74–76} Studies have also examined IV injection of ASCs for repair of the liver,⁷⁵ heart,⁷⁷ endothelium,⁷⁸ and even olfactory epithelium.⁷⁹ An emerging area of investigation involves IV administration of ASCs for autoimmune and inflammatory disorders, such as experimental colitis and abdominal sepsis,^{80–82} muscular dystrophy,⁸³ experimental arthritis,⁸⁰ and encephalomyelitis.⁸⁴ Two provocative case studies have also been published showing beneficial outcomes of IV-delivered ASCs in humans: the first in rheumatoid arthritis, and the second in chronic autoimmune thrombocytopenia,^{85,86} indicating that IV ASCs may be a safe and beneficial future therapeutic modality.

In vitro: protocols on differentiation

Osteogenic differentiation (Fig. 12.10)

For osteogenic differentiation, cells should be plated in a six-well plate at a density of 100 000 cells per well, in 12-well plates at a density of 50 000 cells per well, or in a 24-well plate at 25 000 cells per well. After attachment, ASCs are treated with osteogenic differentiation medium (ODM) containing Dulbecco's modified eagle medium (DMEM), 10% FBS, 100 µg/mL ascorbic acid, 10 mM β-glycerolphosphate, and 100 IU/mL penicillin/streptomycin. This differentiation medium can be enhanced with the supplementation of several cytokines, such as insulin-like growth factor, platelet-derived growth factor (PDGF), or BMP-2 to stimulate increased osteogenesis.^{87,88} ODM should be replenished every 3 days.

Early and late osteogenic differentiation have been defined at time points that differ across species. Whereas mASCs undergo early osteogenesis by day 7 and late osteogenesis by day 14, hASCs undergo much more robust osteogenesis with early osteogenesis by day 3 and late osteogenesis by day 7. To assess osteogenic differentiation, RNA from ASCs

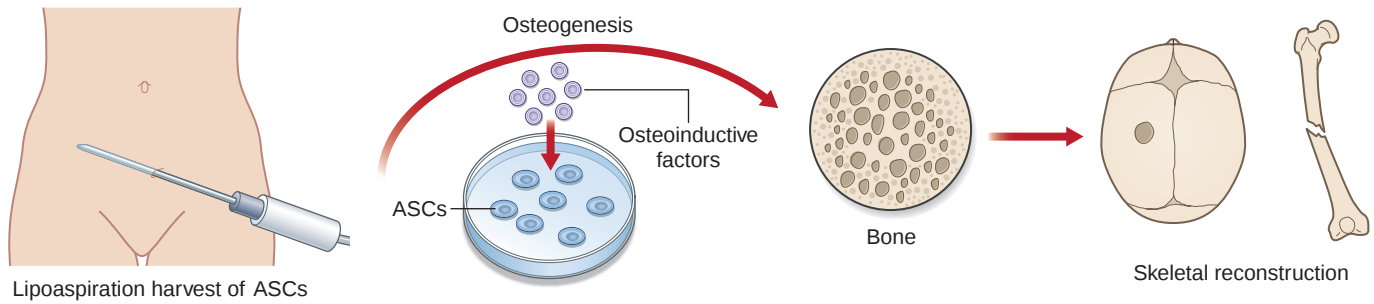


Fig. 12.10 Potential clinical uses for liposuction-acquired fat. Adipose-derived stromal cells (ASCs) are harvested by liposuction (left), cultured *in vitro* with differentiation medium (middle) to bone, and subsequently utilized for reconstructive procedures treating a myriad of diseases (right).

can be analyzed. Specific gene markers of osteogenic differentiation include osteocalcin (*OCN*), osteopontin (*OPN*), runt-related protein-2 (*Runx2*), collagen Ia (*COL1A*), and alkaline phosphatase (*ALP*). *ALP* staining and quantification can also be performed on day 3 of differentiation to assess early osteogenic activity (Fig. 12.11). Subsequently, late osteogenic activity can be assessed at day 7 of differentiation by alizarin red staining, which detects extracellular mineralization.

Adipogenic differentiation (Fig. 12.12)

To stimulate differentiation of ASCs towards mature adipose tissue, cells are seeded in a similar density as described for osteogenic differentiation. Adipogenic differentiation medium, which contains 10 $\mu\text{g/mL}$ insulin, 1 μM dexamethasone, 0.5 mM methylxanthine, and 200 μM indomethacin, is added to the cells. At 3 days, the medium should be replaced with 10 $\mu\text{g/mL}$ insulin. Differentiation can be assessed by oil



Fig. 12.11 Genes involved in differentiation of a bone progenitor cell to an osteoblast. Lineage-specific differentiation is associated with the ordered sequence expression of various genes. Osteoblast differentiation is associated with expression of runt-related protein-2 (*Runx2*), alkaline phosphatase (*ALP*), osteopontin (*OPN*), and osteocalcin (*OCN*), corresponding with early, intermediate, and late osteogenesis.

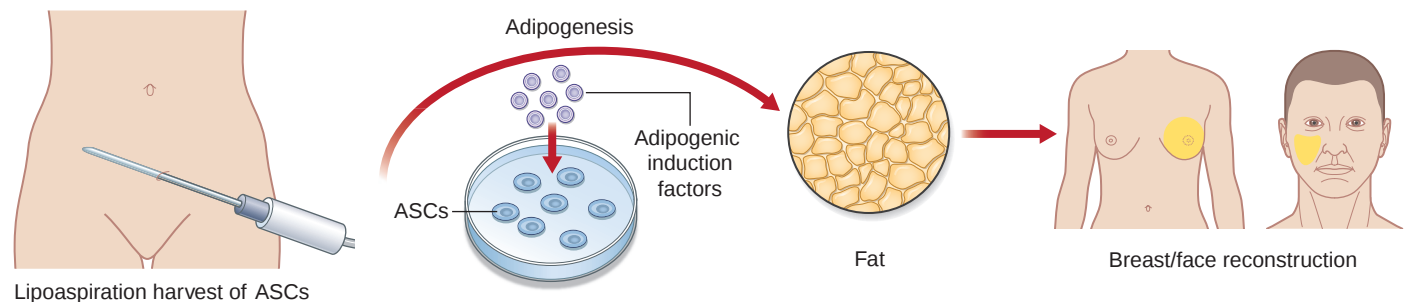


Fig. 12.12 Potential clinical uses for adipocyte differentiation of human adipose-derived stromal cells (ASCs). ASCs are harvested by liposuction (left), cultured *in vitro* with differentiation medium (middle) to fat, and subsequently utilized for reconstructive procedures treating soft-tissue defects (right).

red O staining and quantification or gene analysis. Specific genes expressed by adipose tissue during differentiation include *GCP1*, lipoprotein lipase (*LPL*), and peroxisome proliferation-activated receptor γ (*PPAR\gamma*; Fig. 12.13).

Chondrogenic differentiation

Chondrogenic differentiation is difficult to perform in monolayer and is thus performed using micromass cell droplets. Each 10 mL droplet contains 100,000 cells, which are seeded in culture dishes and allowed to form cell aggregates and substratum at 37°C for 2 hours. Chondrogenic medium includes DMEM, 1% FBS, 1% penicillin/streptomycin, 37.5 mg/mL ascorbate-2-phosphate, ITS (insulin, human transferrin, and selenous acid) premix, and 10 ng/mL transforming growth factor- β_1 (*TGF- β_1*). This medium is carefully added around the cell aggregates. By 24 hours, the aggregates should coalesce and become spherical. Micromasses are fixed with 4% paraformaldehyde/4% sucrose and embedded at day 3 and day 6 for histological analysis. Alcian blue allows for staining of chondrogenic tissues and glycosaminoglycan assays allow for quantification of chondrogenesis. Subsequent gene analysis can be performed using chondrogenic gene analysis such as *SOX-9*, aggrecan, and collagen II.

In vivo model

Nude athymic mouse 4 mm calvarial defect

To translate *in vitro* findings to the clinical realm, robust *in vivo* data must be obtained to demonstrate the osteogenic



Fig. 12.13 Adipocyte differentiation is associated with expression of lipoprotein lipase (LPL), peroxisome proliferator-activated receptor ($PPAR\gamma$), and enhancer-binding proteins (EBPs).

capacity of ASCs. *In vivo* models should include large immunocompetent animals such as sheep⁸⁹ and dogs,^{90,91} as well as smaller immunocompromised animals such as rabbits,⁹² rats,⁹³ or mice.²⁸ Though several models exist to determine *in vivo* osteogenic healing, we prefer the nude mouse model as it is reliable and easily reproducible. Immunocompromised animals such as nude athymic mice allow scientists to assess the effect of ASCs on an area while decreasing the innate immune response to xenotransplanted cells that can confound results. Mice are readily available in large quantities and can be studied by most small animal imaging technologies such as micro-computed tomography (micro-CT), micro-positron emission tomography (micro-PET), and bioluminescent imaging (BLI). Mice, however, heal wounds rapidly and effectively and thus scientists must demonstrate that any result is superior to the animal's baseline healing capacity. One way to demonstrate an effect is to create a defect so large that it overwhelms the animal's innate ability to heal the wound. This large defect is referred to as "critical-sized" and does not heal even over time. An example of this type of defect that we have utilized in an *in vivo* model is a 4 mm defect in the parietal bone of a nude athymic mouse.⁷²

Non-healing, critical-sized (4 mm) calvarial defects can be created in the right parietal bone of adult male CD-1 nude mice using a high-speed dental drill. After cleaning the surgical site with Betadine, an incision is made just off the sagittal midline to expose the right parietal bone. The pericranium is then removed using a sterile cotton swab. Using diamond-coated trephine bits and saline irrigation, unilateral full-thickness critical-sized calvarial defects are created in the non-suture-associated right parietal bone. It is important that the dura mater be left undisturbed as studies, including a 2011 study by Levi *et al.* suggest that cell-cell interactions between dura mater and engrafted ASCs may be crucial in stimulating osteogenic repair (Fig. 12.14). In preparation for implantation, scaffolds can be seeded with hASCs 24 hours prior to implantation. For scaffold creation, apatite-coated PLGA scaffolds were fabricated from 85/15 poly(lactic-co-glycolic acid) by solvent casting and a particulate leaching process. Briefly, PLGA/chloroform solutions were mixed with 200–300 μ m diameter sucrose to obtain 92% porosity (volume fraction), and compressed into thin sheets in a Teflon mold. After freeze-drying overnight, scaffolds were immersed in ddH₂O to dissolve the sucrose, and gently removed from the Teflon plate for disinfection and drying.

For apatite coating, simulated body fluid (SBF) solution was prepared by sequentially dissolving CaCl₂, MgCl₂·6H₂O, NaHCO₃, and K₂HPO₄·3H₂O in ddH₂O. Solution pH was lowered to 6 by adding 1 M hydrochloric acid to increase

solubility. Na₂SO₄, KCl, and NaCl were added and the final pH was adjusted to 6.5 (SBF 1). Mg²⁺ and HCO₃⁻ free SBF (SBF 2) was prepared by adding CaCl₂ and K₂HPO₄·3H₂O in ddH₂O and pH was lowered to 6. KCl and NaCl were added and the final pH was adjusted to 6.8. All solutions were sterile-filtered through a 0.22- μ m polyethersulfone (PES) membrane (Nalgene, NY). The obtained PLGA scaffolds were incubated in SBF 1 for 12 hours and switched to Mg²⁺ and HCO₃⁻ free SBF 2 for another 12 hours at 37°C under gentle stirring. Coated scaffolds were washed with ddH₂O to remove excess ions and lyophilized prior to use.

We found 150 000 cells/scaffold to be optimal in our laboratory.⁷³ The hASCs to be seeded onto each scaffold are first suspended in 25 μ L of growth media and placed onto the scaffold for 30 minutes. The scaffold is subsequently submerged in 100 μ L of growth media for 12 hours of incubation. Before implantation, cell-seeded scaffolds should be rinsed in sterile PBS to prevent transfer of medium-derived growth factors.

Clinical correlates

Recent case studies have focused on the use of hASCs to replace bone loss.⁹⁴ In case reports, defects of the calvaria,⁹⁵ maxilla,⁹⁶ and mandible⁹⁷ have either healed or been enabled to heal more rapidly with the use of hASCs. Such reconstructions eliminate the need for alloplastic materials and thus reduce the risk of infection, breakdown, or rejection. Despite increasing evidence from translational research, there is a paucity of data defining the mechanisms through which hASCs influence an osseous defect. Do hASCs directly form bone to heal a skeletal defect? Or do engrafted hASCs function as efficient factories to produce potent pro-osteogenic

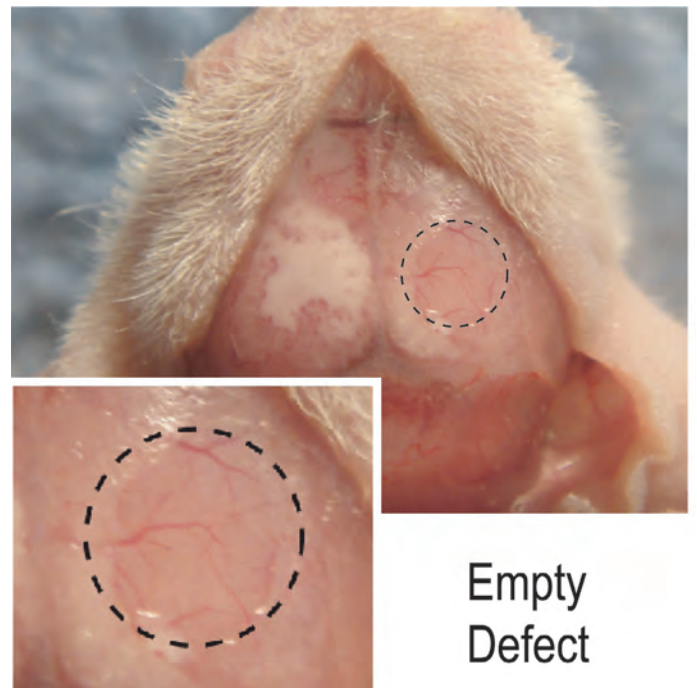


Fig. 12.14 A 4-mm non-healing critical-sized defect in the right parietal bone of a CD-1 nude athymic mouse.

cytokines? In the case of our calvarial defect model, careful examination of calvarial defects engrafted with ASCs yields profitable insights into the potential derivation of healing. For example, bone is often observed to mineralize from the edges of a cranial defect inwards, which suggests that the host calvarium may contribute to the bony regenerate. Concurrently, small, isolated islands of bone are often observed early postoperatively, which suggests either contribution from engrafted ASCs or from host dura mater (another source of significant osteogenic progenitors).^{98–100} Finally, uniform and thorough healing of hASC-engrafted defects suggests that primary osseous healing is derived from the engrafted donor cells themselves. It is likely that all three cell types (donor ASCs, host calvarial osteoblasts, and host dura mater) contribute to bony healing.

Future direction of tissue engineering using ASCs

We believe that major breakthroughs in aesthetic and reconstructive surgery using autologous tissue will not come by incremental improvements to technical aspects such as liposuction cannulas or injection syringes. Instead, novel cell-based strategies must be explored to identify and isolate specific fat precursors from hASCs and to coordinate the physiologic induction of adipose tissue differentiation in a biomimetic environment *in vivo* (Fig. 12.15). However a significant gap exists between the current knowledge regarding ASC biology and their future translation to clinical use. First, the safety of hASCs must be determined. Potential oncogenic transformation must be inhibited so that tumors of mesodermal origin are not produced after cell engraftment.⁷⁶

hASC-seeded biomaterial constructs may constitute an optimal delivery method for autologous fat transfer by facilitating the assembly of natural three-dimensional adipose, cartilage, or bone tissues.¹⁰¹ Our ultimate translational goal is to harvest subcutaneous adipose tissue, isolate ASCs, and implant these cells on an osteoconductive and/or osteoinductive scaffold into the skeletal defect within the course of a single operative procedure without leaving the operating room (Fig. 12.16).

Bone marrow mesenchymal stem cells

Definitions

Bone marrow MSCs are multipotent adult stem cells that have been shown to differentiate into a variety of cell types, including adipocytes, chondrocytes, osteocytes, skeletal myocytes, and cardiomyocytes. Numerous studies have documented MSC plasticity, immunomodulatory properties, and potential for use in tissue engineering strategies. MSCs have also been found to be recruited to sites of injury, where they may participate in the body's own natural system of tissue repair. These findings highlight the enormous potential for MSCs in clinical use for an increasing range of medical disorders. While some debate remains over the effect of MSCs in various disease states, their prospects for use as an "off-the-shelf" biological therapeutic remains a tangible goal.

The role of MSCs within bone marrow has been debated, with work by Prockop and others helping to elucidate functions both intrinsic and extrinsic to the bone.^{7,102} By infusing

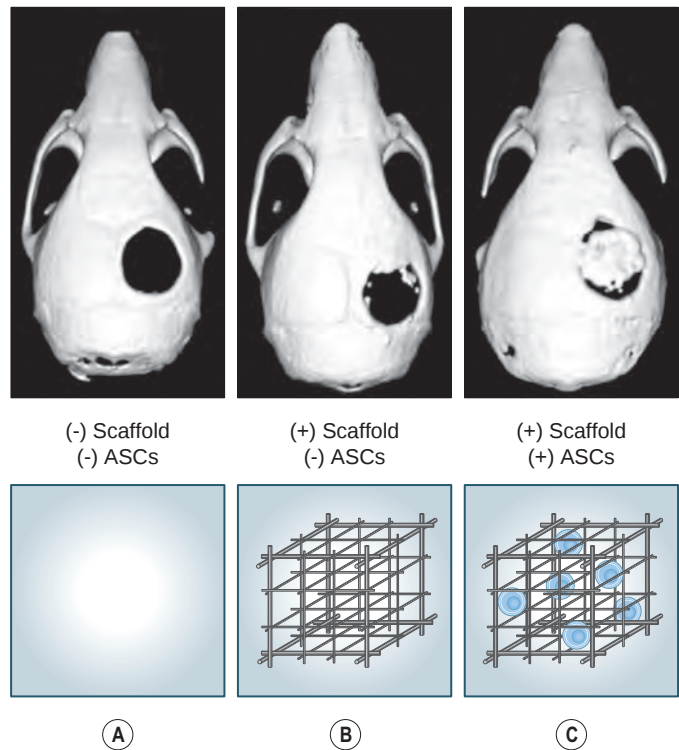


Fig. 12.15 Utilization of adipose-derived stromal cells (ASCs) to heal a skeletal defect. **(A–C)** Micro-computed tomography images of a 4-mm critical-sized mouse parietal bone defect in nude CD-1 mice. **(A)** Without either a scaffold or ASCs, this defect will not heal by 2 weeks. **(B)** Scaffold only. Wounds treated with scaffold alone also show minimal healing. **(C)** Scaffold with ASCs. Significant re-mineralization is observed after only 2 weeks post-injury in wounds treated with ASC-seeded scaffolds.

genetically marked MSCs into isogenic mice, studies revealed a distribution of these cells to various locations, including cortical and cancellous bone, cartilage, spleen, thymus, lung, and liver.⁷ MSCs thus demonstrate the ability to circulate and participate in normal cellular turnover even outside of hematopoietic tissues.

Current concepts and research

In recent years, the potential use of MSCs in therapeutic modalities for tissue repair has become increasingly promising. As such, a number of studies have focused on phenotypically characterizing these cells both *in vitro* and *in vivo*. The initial isolation of MSCs exploited their ability to adhere to plastic. However, many of the clones isolated by Friedenstein's method proved incapable of osteogenic differentiation.^{103,104}

This suggested that a considerably heterogeneous population of cells exists within the marrow stroma. Percoll gradients, as employed by Pittenger *et al.*,¹³ Caplan,¹⁰⁵ and Haynesworth *et al.*,¹⁰⁶ allowed for a more homogeneous population of MSCs to be harvested, as confirmed by flow cytometric analysis of cell surface antigens. Alternative methods to obtain higher degrees of homogeneity have also been attempted, including culturing MSCs in low oxygen tension.^{107,108} Perhaps the most rigorous means by which to define MSCs has been through the use of cell surface antigens expressed *in vitro*. The International Society for Cellular Therapy announced

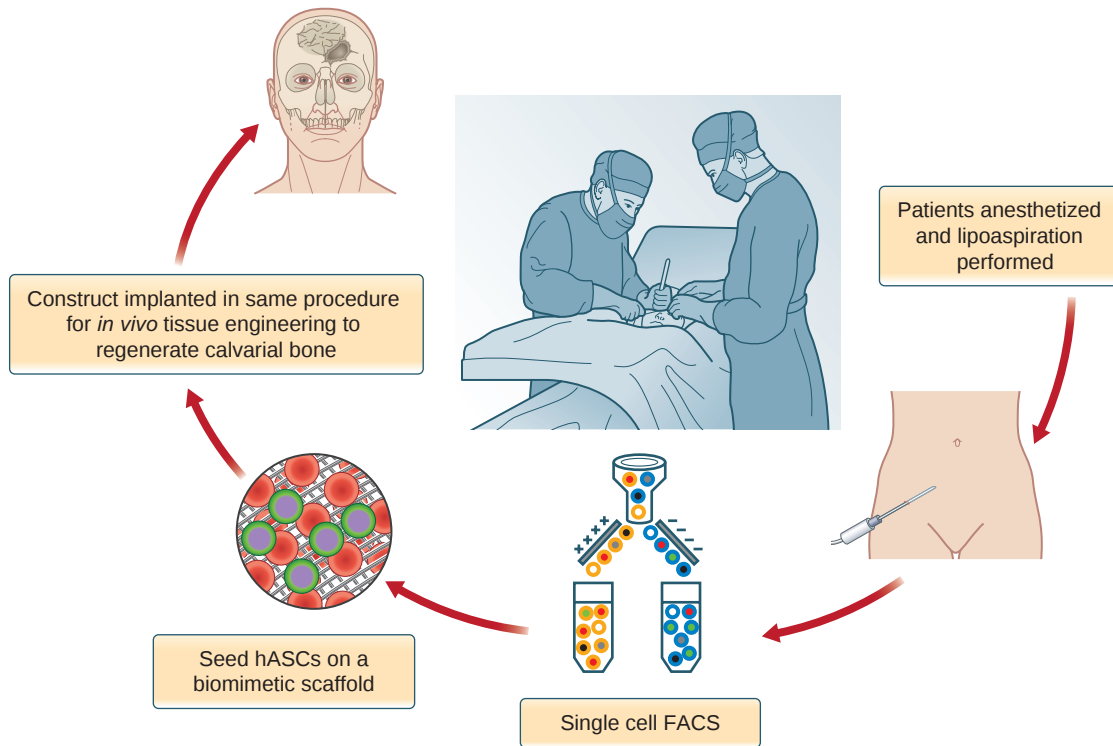


Fig. 12.16 Ultimate clinical translational goal: taking patient to the operating room and harvesting a multipotent, self-renewing cell population such as human adipose-derived stromal cells (hASCs), and then placing them on a scaffold for reconstruction of a tissue defect. FACS, fluorescence-activated cell sorting.

specific criteria to define bone marrow MSCs in 2006.¹⁰⁹ Based on these criteria, MSCs are required to be plastic-adherent when maintained in standard culture conditions and to express CD73 (ecto 5'-nucleotidase), CD90 (Thy-1), and CD105 (Endoglin) while lacking expression of CD45 (protein tyrosine phosphatase), CD34 (hematopoietic cluster differentiation molecule 34), CD14 (macrophage/neutrophil cluster differentiation molecule 14), CD19 (follicular dendritic cell/B-cell cluster differentiation molecule 19), and human leukocyte antigen (HLA)-DR. Furthermore, MSCs must be capable of differentiation into adipocytes, chondroblasts, and osteoblasts *in vitro*. While these criteria continue to evolve, they have served as a minimum standard for more recent investigations.

While the *in vitro* characterization of MSCs has progressed, phenotypic delineation of these cells *in vivo* has advanced at a much slower pace and collective data remain far from complete. More recently, investigators enriched the STRO-1 fraction through additional positive selection for CD106 (vascular cell adhesion molecule-1: VCAM-1) and CD146 (melanoma cell adhesion molecule), obtaining a purified fraction capable of self-renewal and multipotent differentiation.¹¹⁰ These findings lend further support to the notion that MSCs function as an *in vivo* stem cell source for derivation of mesenchymal tissue.

The lineage of MSCs and HSCs has also been carefully evaluated by investigators looking to determine whether MSCs and HSCs exist as different populations within bone marrow. Through sex-mismatched HLA-identical bone marrow allografts, researchers have demonstrated that marrow-derived stromal cells are exclusively host-derived

while HSC-derived macrophages originate from donors.¹¹¹ This finding indicates that MSCs existing within the stromal fraction are distinct from hematopoietic cells. Contemporary models thus identify at least two types of stem cells within the bone marrow, with HSCs giving rise to hematopoietic cell types and osteoclasts, while MSCs differentiate into a multitude of mesenchymal lineages. Furthermore, it is widely believed that MSCs are derived from mesoderm and that, as these cells stain positive for angiopoietin-1, they likely reside with pericytes located along the walls of sinusoidal blood vessels in bone marrow.^{112,113}

Recent investigations have identified an extraordinary property of MSCs with important therapeutic implications. Although still poorly understood, MSCs have been found to possess immunomodulatory properties.^{114–119} Baseline expression of MHC class I proteins has been detected in MSCs while MHC class II proteins are entirely absent.¹²⁰ This particular profile has been associated with non-immunogenic conditions, thus potentially allowing for MSC transplantation into allogeneic hosts without the requirement of immunosuppressive therapy.¹²¹ Even more surprising, MSCs have been found to be capable of modulating T-cell function.^{114,115,117,119} In co-culture conditions, MSCs have been shown to decrease expression levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha, interferon-gamma, interleukin-4, and interleukin-10 in dendritic cells and helper T cells.¹¹⁵ MSC secretion of interleukin-1 receptor antagonist has also been reported to contribute to overall MSC-mediated immunosuppression.¹²² From a clinical perspective, these properties may one day be exploited for treatment of conditions such as graft-versus-host disease and autoimmune disorders.^{121,123}

***In vitro*: protocols on tissue harvest and differentiation**

Contemporary technologies to harvest and culture MSCs still utilize the same fundamental property of adherence to plastic employed by Friedenstein *et al.* over 40 years ago.⁸ More recently, investigators have incorporated the use of density gradients to increase homogeneity and eliminate unwanted cell types present in marrow aspirate.¹³ Human MSCs are commonly harvested from the iliac crest.¹²⁴ Murine MSCs, in contrast, can be harvested from either fibula or tibia by first flushing the marrow contents out with a 27G syringe.¹²⁵ Harvested bone marrow is then placed in an aqueous solution of highly branched hydrophilic polysaccharides. By centrifuging for 30 minutes, four layers become visible. Red blood cells may be found in the bottom layer, polysaccharide solution may be found in the second layer, the third layer contains the majority of mononuclear cells, and the top layer contains primarily acellular medium. It is the third layer (mononuclear cells) that is isolated, re-centrifuged, and plated on to plastic culture dishes. MSC colonies may often be observed to form on these dishes after 6–8 days of *in vitro* culture.

Lineage-specific culture conditions that induce differentiation of MSCs into adipocytes, chondrocytes, osteoblasts, and myoblasts have been well described. Adipogenic differentiation can be induced by treatment of MSCs with 1-methyl-3-isobutylxanthine, dexamethasone, insulin, and indomethacin.¹³ Fat accumulation can be readily appreciated histologically by the formation of lipid-rich vacuoles within cells. In addition, differentiated MSCs have been shown to express various markers of adipogenic differentiation, including *PPAR* γ 2, *LPL*, and fatty acid-binding protein aP2 (see Fig. 12.13). To promote chondrogenic differentiation, MSCs are cultured serum-free in a pelleted “micromass” with TGF- β ₃.¹³ A proteoglycan-rich extracellular matrix can be observed along with expression of type II collagen after 2 weeks, both of which are typically found in articular cartilage. Osteogenic differentiation of MSCs can be accomplished with the same components as described in the previous section on ASCs. Finally, culture of MSCs with dexamethasone and hydrocortisone has been shown to induce expression of key regulatory factors for myogenic differentiation, including *MyoD*1 and myogenin.¹²⁶

***In vivo* models**

The ability for MSCs to differentiate along several lineages has made these cells excellent candidates for the repair and regeneration of many tissues. The multipotency of MSCs, along with their ease of isolation and expansion potential, has led to a variety of preclinical studies evaluating their use in treating cardiovascular disease, central nervous system injury, diabetes, and bone/cartilage regeneration.

Cardiovascular disease remains one of the leading causes of morbidity and mortality worldwide, accounting for nearly 20 million deaths annually.¹²⁷ Contemporary approaches to treatment have centered on preservation of myocardium through pharmacologic therapy and revascularization. The ability for MSCs to undergo transdifferentiation along a cardiomyogenic lineage has sparked recent interest in their application for post-infarct myocardial regeneration.¹²⁸ Importantly, *in vivo* studies have demonstrated that injected

MSCs preferentially migrate to sites of inflammation, thereby allowing for their potential participation in repair of injured cardiac muscle.¹²⁹ Myocardial ischemia may promote release of chemo-attractive factors, increase vascular permeability, and enhance expression of adhesion proteins to allow for proper homing of MSCs. A 2015 randomized, double-blind, placebo-controlled trial conducted by Mathiasen *et al.* found that intra-myocardial injections of MSCs decreased left ventricular end systolic volume (LVESV) in patients suffering from New York Heart Association heart failure classes II–III with ejection fraction <45%. In contrast, patients treated with placebo had increased LVESV at six months follow-up. No adverse effects were identified during the course of the study. They concluded that intra-myocardial injections of autologous culture-expanded MSCs were safe for clinical use and improved myocardial function in patients with severe ischemic heart failure.¹³⁰ How these cells truly act at post-infarct sites, however, remains controversial.

Like myocardial infarction, injury to the central nervous system has also contributed to significant death and disability worldwide. As investigators have shown MSCs to be capable of undergoing transdifferentiation into ectoderm-derived neuronal tissue, MSC use in various animal models of stroke has yielded provocative findings.¹³¹ Several studies have demonstrated that injected MSCs can migrate to sites of stroke injury and differentiate into cells expressing neuronal markers.^{132–134} Preliminary reports in rats have also shown that MSCs may potentially restore damaged neurons.^{133,134} From a functional perspective, improved sensorimotor function has been detected following injection of MSCs into sites of cortical ischemia.¹³⁵

The treatment of diabetes has been another field where use of MSCs has provided some promising results. Presently, type 1 diabetes may be partially reversed through the replacement of functional pancreatic β cells. Unfortunately, islet cell transplantation has been limited by immune rejection and continued autoimmune-mediated destruction.¹³⁶ The scarcity of donor islet cells further obstructs treatment of this disease. The potential ability of MSCs to modulate the immune system and undergo *in vitro* β -cell transdifferentiation has led to several preclinical investigations employing these cells in animal models of diabetes.^{136–139} As with cardiac ischemia and stroke, however, the true role of MSCs in ameliorating hyperglycemia remains controversial. Introduction of human MSCs into immunocompromised diabetic mice was found to upregulate only mouse insulin production. This suggests that MSCs promote regeneration of endogenous islets but do not undergo transdifferentiation and integration into the host pancreas.¹³⁹ Nonetheless, these findings indicate that MSCs may one day represent a viable therapeutic option for the treatment of type 1 diabetes.

The potential use of MSCs most germane to the field of plastic and reconstructive surgery remains the utilization of these cells in bone and cartilage regeneration. Bone homeostasis represents a careful balance between bone production by mesenchymal lineage osteoblasts and bone resorption by hematopoietic lineage osteoclasts.¹²¹ MSCs potentially alter this balance through the modulation of receptor activator of nuclear factor- κ B ligand (RANKL) and osteoprotegerin expression.¹²¹

It has been suggested that a loss of MSC function may contribute to reduced bone regeneration with age.¹⁴⁰ MSCs

have thus been evaluated as potential cellular building blocks for tissue engineering strategies. Using a canine femoral critical-sized defect model, investigators have shown MSCs to be capable of regenerating bone when loaded onto a hydroxyapatite-tricalcium phosphate cylinder.^{90,91,141} Sixteen weeks after introduction of MSCs, histological analysis revealed new bone spanning the entire defect.⁹¹ In addition, both autologous and allogeneic MSCs were found to yield equivalent results with no lymphocytic infiltration or antibody formation noted when leukocyte antigen-mismatched allogeneic cells were implanted.⁹¹

Vascular composite allotransplantation (VCA), including osseous defects, is another growing area of interest in reconstructive surgery. Interestingly, MSCs have been shown in animal models to increase regulatory T-cell levels and prolong survival of immunogenic skin-bearing VCA osseous grafts when combined with a short course of immunosuppression.¹⁴²

Apart from the appendicular skeleton, investigators have also studied the use of MSCs in promoting bone formation for the spine. Spinal fusion remains the last resort for degenerative disc disease and over 300 000 cases are operated on annually in the US.¹²¹ Current research has focused on improvement of spinal fusion through the combination of autologous bone marrow with synthetic scaffolds and cytokine therapy. MSCs implanted on Matrigel and placed into the lumbar fusion bed of rats have been shown to result in a greater rate of successful fusion compared to animals receiving only mixed-marrow stromal cells.¹⁴³ Kai *et al.* reported similar results in rabbits using a combination of MSCs, calcium phosphate ceramic blocks, and recombinant human BMP-2.¹⁴⁴ These results suggest that MSCs may be a suitable replacement for more traditional methods currently employed in iliac crest bone grafting. MSCs may also allow for greater mature osseous tissue formation at earlier time points following spinal fusion.

Repair and regeneration of cartilage remain another challenging problem where MSCs may yield more compelling strategies than those currently available. The ability to treat damaged cartilage and osteoarthritis is currently quite limited with prosthetic joint replacement representing the best contemporary solution. Preclinical trials in goats, however, have shown MSCs to promote cartilage regeneration in knee joints.¹⁴⁵ Following surgical induction of osteoarthritis by excision of the medial meniscus and resection of the anterior cruciate ligament, Murphy and colleagues found that a single injection of MSCs suspended in dilute sodium hyaluronan could result in reduction of articular cartilage degeneration, osteophytic remodeling, and subchondral sclerosis.¹⁴⁵ These findings have also been observed in a mouse model for human rheumatoid arthritis where allogeneic MSCs introduced intraperitoneally were found to prevent occurrence of severe irreversible damage to cartilage and bone.¹⁴⁶ Rather than directly providing a cellular contribution to cartilage formation, in this instance MSCs were thought to modulate immune responsiveness and expression of inflammatory cytokines.¹⁴⁶

Clinical correlates

The last two decades of research with MSCs in both *in vitro* culture and *in vivo* animal models has allowed scientists to

begin incorporating these cells into clinical trials for an ever-increasing range of potential medical disorders.^{121,123} MSCs have been proposed for the treatment of a wide variety of diseases and patients have already begun enrolling in industry-sponsored studies (Osiris Therapeutics, Waltham, MA) that investigate the use of these cells in graft-versus-host disease, Crohn's disease, and type 1 diabetes. The FDA has also approved the study of autologous MSCs in middle cerebral artery acute stroke treatment. To date, the most prominent application of MSCs in clinical trials has been their use in ischemic heart disease.

Following ischemic insult to the myocardium, reperfusion may salvage large regions of viable muscle, but this is often incomplete, resulting in a process of adverse left ventricular remodeling.¹⁴⁷ As previously noted, preclinical trials have shown that autologous MSCs improve cardiac function modestly either through transdifferentiation or elaboration of trophic factors capable of stimulating endogenous reparative mechanisms.^{148,149}

Similar to ischemic cardiomyopathy, MSCs have also proven to be efficacious in early clinical studies involving skeletal disease. Long-bone distraction osteogenesis is an emerging field in which MSCs have been found to promote improved healing and faster recovery rates.¹⁵⁰ In 17 patients undergoing distraction, injection of MSCs along with platelet-rich plasma into the callus during both lengthening and consolidation phases resulted in accelerated mature bone formation and a reduction in the incidence of complications.^{151,152} Horwitz and colleagues have also investigated the use of MSCs in the treatment of osteogenesis imperfecta, a genetic disorder of type I collagen resulting in fragile bones and skeletal deformities.^{153–155} While there is no current cure for osteogenesis imperfecta, preliminary reports have shown MSCs to be successful in enhancing bone formation in these patients.¹⁵⁴ Children receiving two infusions of allogeneic MSCs were noted to demonstrate engraftment of these cells in multiple sites, including bone and skin. Importantly, accelerated growth velocity was appreciated during the first 6 months following treatment with no associated complications.¹⁵³ These findings reveal that MSCs may be safely administered to children and when injected can localize to genetically defective tissues. Furthermore, MSC therapy has been demonstrated to be safe and effective in small numbers of patients treated with MSCs to ameliorate clinical symptoms of osteoarthritis. The 2015 study found that in patients with severe knee osteoarthritis, the knee injected with MSC had better function at 5 years compared to the knee that was not injected.¹⁵⁶ Another 2015 study expanded on this finding by demonstrating long-term safety and efficacy of intra-articular MSC injection in patients with different osteoarthritic joints (such as hip, knee, and ankle osteoarthritis).¹⁵⁷ In summary, while the human data at present is promising, further studies are needed with larger sample sizes and longer follow-up periods to confirm the clinical benefit and safety of MSC use in bone regeneration. There are myriad clinical trials currently underway to address these important questions, with an excess of 140 clinical trials at various stages of investigation recorded in the US at present.

The breadth of clinical trials involving MSCs is rapidly expanding, as studies have shown these cells to possess a strong propensity to ameliorate a wide range of tissue deficits secondary to injury or disease.

Tissue-specific stem cells

Definitions

Adult stem cells are undifferentiated cells found in almost all tissues and organs after embryonic development¹⁵⁸ and have the capacity for both self-renewal and differentiation into a restricted number of specialized cell types of the tissue or organ in which they are found. Their major function is to maintain homeostasis and ensure that tissue damage resulting from various forms of insult or injury is repaired. It has been hypothesized that defects in adult stem cell function may be responsible for a range of diseases. A study of adult stem cell function could therefore reveal important biological mechanisms that could be exploited for therapeutic purposes.¹⁵⁹

Although rare, adult stem cells serve a critical function within the hierarchical organization of complex tissues and organs. They give rise to replacement cells to maintain tissue integrity throughout development. A model of coexisting quiescent and active progenitor subpopulations has been proposed to describe adult stem cells with different cell cycle states.¹⁶⁰ It is hypothesized that they exist in tightly regulated zones to ensure that differentiated cells can be rapidly repopulated while keeping a quiescent back-up system to maintain the longevity of adult stem cell pools. Another concept which has been studied in adult stem cells is transdifferentiation, or the ability of lineage-directed stem cells to differentiate into tissues or organs from another embryonic lineage.¹⁶¹ For example, studies in mice have demonstrated the ability of bone marrow stem cells to differentiate into multiple cell types.

Current concepts and research

Skin

Mammalian skin is a widely available and readily accessible tissue for the study of adult stem cell function. Gene expression studies have identified critical regulators of epithelial stem cell function, including Wnt/beta-catenin, BMP, notch, and Hedgehog pathways.¹⁶² Furthermore, numerous subtypes of epithelial progenitors have recently been identified and contribute to different skin compartments containing specific resident epithelial stem cells, such as the hair follicle, sebaceous glands, and the interfollicular epidermis (Fig. 12.17).¹⁶³ Hair follicle stem cells are located in the bulge region and cycle slowly under normal conditions. However, following injury they rapidly activate and migrate outwards toward the region of epithelial damage.¹⁶⁴

These epithelial stem cells are located in discrete skin compartments but have common features, which may reveal unifying mechanisms in normal homeostasis. They all express K5, K14, and delta Np63, are adjacent to an underlying basement membrane, and utilize many of the same regulatory signaling pathways.¹⁶⁵ The complex skin environment also houses putative melanocyte stem cells involved in the graying of hair¹⁶⁶ and dermal pericytes which have been implicated as important stem cell regulators of skin regeneration.¹⁶⁷

Many of the mechanisms underlying skin embryogenesis are recapitulated later in adult life to maintain skin homeostasis.¹⁶² Several models have been proposed to explain the balance of stem cell populations and function. One such model describes asymmetric versus symmetric cell division. Symmetric cell

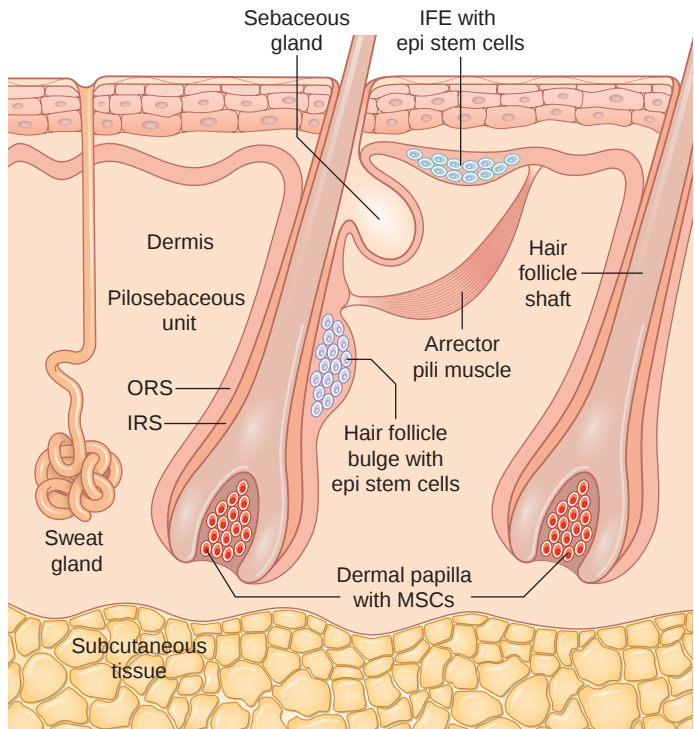


Fig. 12.17 Cells surrounding the hair follicle traffic to a wound site. IFE, interfollicular epidermis; IRS, inner root sheath; MSCs, mesenchymal stem cells; ORS, outer root sheath.

division describes the generation of two daughter cells that eventually acquire the same differentiated fate. Asymmetric division describes the process whereby a stem cell produces one daughter cell with a stem cell fate and another daughter cell destined for differentiation. These models are not mutually exclusive and are both thought to play an important role in the maintenance of skin stem cell populations.¹⁶⁸

Bone

Osteoblasts are derived from bone marrow MSCs and their differentiation pathways have been well studied. These cells form bone, regulate bone growth and remodeling, and differentiate into mature osteocytes in response to stimuli such as mechanical loading, hormones, and cytokines.¹⁶⁹ A delicate balance is maintained with their osteoclast counterparts, which resorb bone and are derived from monocyte/macrophage precursors. During adult osteogenesis, bone formation proceeds through two different pathways: intramembranous ossification (e.g., skull) or endochondral ossification (e.g., long bones). The former occurs directly from MSC condensation while the latter involves an intermediate MSC-mediated cartilage formation step followed by replacement with bony matrix (Fig. 12.18).¹⁷⁰

Osteoblast differentiation is regulated by several major signaling pathways such as Wnt, BMP, FGF, Hedgehog and transcription factors such as Runx2, Osterix, ATF4, and TAZ.¹⁷¹ These signals determine the fate of skeletal lineage precursors and can be manipulated to induce bone regeneration. BMP-2, -4, and -7 have been successfully used to induce osteoblast differentiation and matrix formation *in vivo* and vehicles for BMP gene delivery such as plasmids and viruses have been effectively employed.¹⁷² Combination gene delivery has been

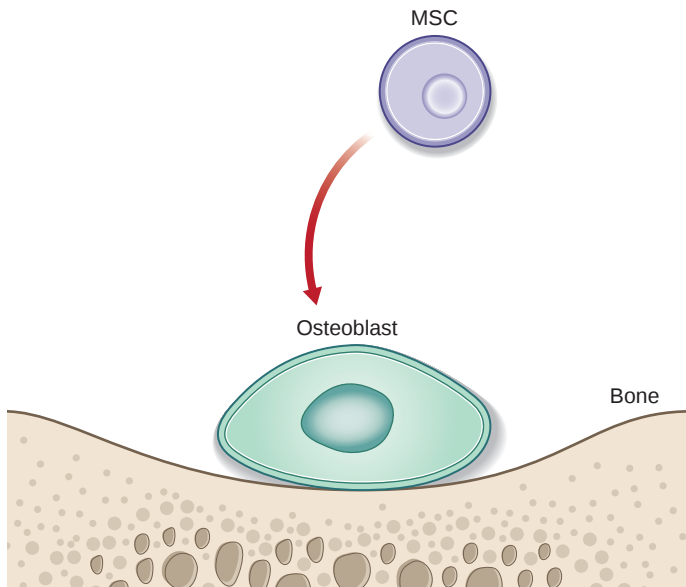


Fig. 12.18 Mesenchymal stem cell (MSC) condensation into an osteoblast as in intramembranous ossification.

successful and is thought to recapitulate more closely the signaling environment *in vivo*, providing a synergistic stimulus for bone formation. This sensitization effect has been demonstrated with combinations of BMPs, vascular endothelial growth factor (VEGF), RANKL, and Runx2 delivery.¹⁷²

Blood vessels

Regulated blood vessel development in response to tissue injury or ischemia is critical for maintenance of healthy tissues. Dysfunction in this neovascularization process often results in disease.¹⁷³ For example, adequate wound healing requires a robust vascular response to deliver immune cells and metabolic substrates necessary for tissue regeneration.¹⁷⁴ In addition, a coordinated pattern of neovascularization signaling and stem cell recruitment is essential for normal organ development during embryogenesis,¹⁷⁵ as well as for tumor growth and metastasis.¹⁷⁶ During embryogenesis, mesoderm-derived angioblasts organize via vasculogenesis to form blood vessels.¹⁷⁷ It was initially believed that all subsequent blood vessel growth occurred through sprouting of pre-existing endothelial cells in a process known as angiogenesis

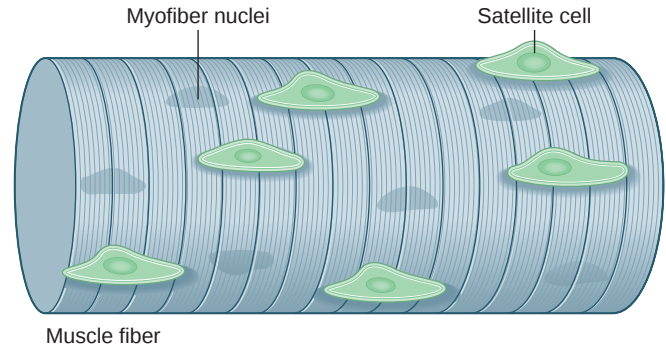


Fig. 12.20 Muscle satellite cells located between muscle fibers and their basement membrane.

(Fig. 12.19).¹⁷⁸ However, it has been discovered that the vascular programming evident during embryonic development is recapitulated in various postnatal states during a process known as adult vasculogenesis (see Fig. 12.19).¹⁷⁹

Endothelial precursor cells (EPCs), which are bone marrow-derived progenitor cells that participate in adult vasculogenesis, were first identified by Asahara *et al.*¹⁸⁰ These cells are recruited to the site of ischemia and divide to form syncytial masses, which tubularize and canalize to form a patent vascular network.¹⁸¹ Pericytes, which retain the pluripotency of MSCs,¹¹² are also intimately involved in vascular morphogenesis. They reside at the interface between endothelial cells and the surrounding tissue and produce pro-angiogenic signals that regulate endothelial cell differentiation and growth.¹⁸² Through both direct physical interaction and paracrine signaling, endothelial cells and pericytes engage in complex crosstalk that is essential for normal vasculogenesis.¹⁸³

Muscle

Satellite stem cells were first described by Mauro in the 1960s as mononucleated cells situated between muscle fibers and their basement membrane (Fig. 12.20).¹⁸⁴ Though different modes of asymmetric cell division have been proposed to regulate satellite cell self-renewal,^{185,186} symmetric cell division is believed to play a major role in the response to muscle injury or when large amounts of myogenic cells are needed to replace missing or dysfunctional muscle mass.¹⁸⁶ Repair mechanisms are also thought to involve recruitment of neighboring satellite cells and circulating myogenic stem cells. In addition, satellite cell dysfunction has been proposed

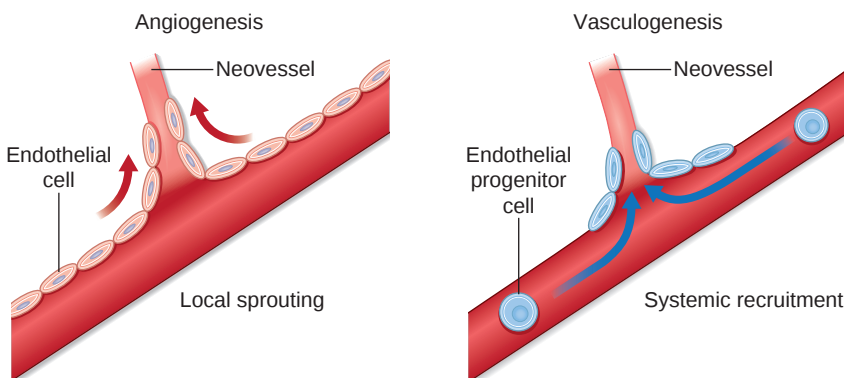


Fig. 12.19 Sprouting of pre-existing endothelial cells in a process known as angiogenesis (left). Formation of new vessel from circulating endothelial progenitor cell known as vasculogenesis (right).

to underlie certain muscular diseases such as Duchenne muscular dystrophy, but this hypothesis requires further study.

The major components of the satellite cell niche are: the adjacent muscle fiber (including the mechanical, electrical, and biochemical signals which emanate from it), the basal lamina, and the microvasculature. These interrelated components regulate the activity of muscle stem cell populations and include calveolin-1, sphingomyelin, calcitonin receptors, the transmembrane protein Megf10, Notch signaling, and matrix components such as proteoglycans.¹⁸⁶

Peripheral nerve

Although peripheral nerves have the capacity to regenerate axons following injury, outcomes after repair remain poor due to direct neuronal damage, as well as chronic denervation of the distal end.¹⁸⁷ However, when denervated supporting Schwann cells are replaced with healthy ones at the site of injury, nerve regeneration is improved (Fig. 12.21). This suggests that cell-based therapies may have an important role in treating nerve injuries. Guenard *et al.* demonstrated that syngeneic Schwann cells could effectively improve nerve regeneration in rat sciatic nerve injuries.¹⁸⁸ Murakami *et al.* transplanted neural stem cells obtained from the hippocampus of rat embryos into sciatic nerve defects and demonstrated nerve regeneration after 8 weeks.¹⁸⁹ Mean number of myelinated fibers and fiber size were increased compared to controls.

Neurotrophic growth factors have also played an important role in experimental models of nerve repair. These include NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, FGF, and PDGF, amongst others.¹⁹⁰ Neurotrophic growth factors are delivered through matrix/conduit release or mini-pump systems but bioavailability throughout the necessary regenerative time scales remains an issue.

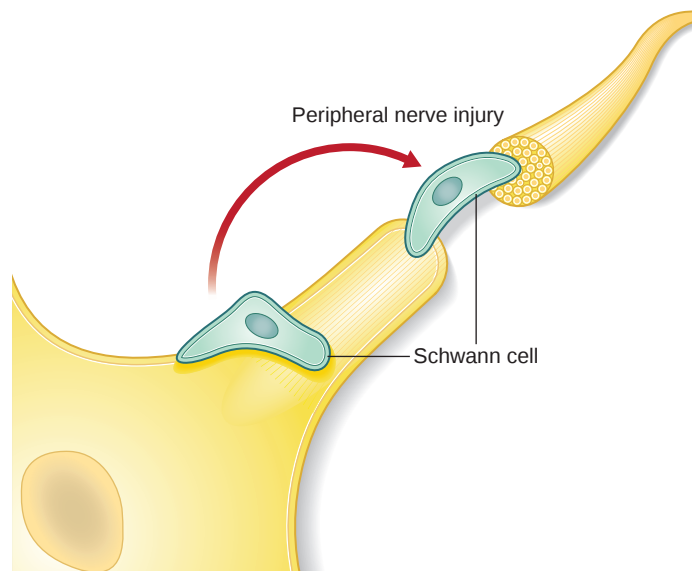


Fig. 12.21 Schwann cell migration to peripheral nerve injury site to assist in repair.

Clinical correlates

Skin

Cell-based therapies have been used for decades in the treatment of burn injury. Autologous epidermal sheets have been grown *ex vivo* and re-implanted into patients with varying degrees of success.¹⁹¹ Bone marrow and fat-derived MSC therapies have proven useful for chronic wounds in the clinical setting, although these are mostly case reports.¹⁹² Dash *et al.* reported a randomized clinical trial using autologous bone marrow MSCs to treat chronic non-healing ulcers.¹⁹³ In this study, stem cell-treated patients demonstrated improvements in pain-free walking and reductions in ulcer size up to 12 weeks post-treatment.

Transplantation of HSCs from peripheral blood and bone marrow has also demonstrated engraftment of cells into skin.¹⁹⁴ Histological evaluation of skin specimens from sex-mismatched transplants showed that up to 7% of cells were XY-positive, indicating that circulating stem cells could differentiate into mature epithelium. However, another study with a similar sex-mismatched transplant design failed to show donor stem cell contribution to keratinocyte populations.¹⁹⁵ Badiavas and Falanga reported on 3 patients with chronic lower extremity wounds refractory to standard therapy who were treated with autologous bone marrow stem cells.¹⁹⁶ Complete wound closure was observed in all 3 patients and there was less wound fibrosis compared to pretreatment wound specimens. It appears that numerous adult stem cell populations can contribute to skin regeneration but the optimal combination of cells and signals remains unknown.

Bone

As previously mentioned, allogeneic bone marrow-derived stem cells transplanted with around 2% donor cell engraftment were shown to improve osteogenesis in three children with osteogenesis imperfecta.¹⁵⁴ Three months after treatment, all patients had increased total bone mineral content, growth velocity, and reduced frequency of bone fracture. In addition, MSCs have shown great promise in early clinical trials in the symptomatic improvement of osteoarthritis in multiple joints as described in a previous section,^{156,157} and osteonecrosis of the femoral head.^{197–199} For instance, a study published in 2015 by Daltro *et al.* found that autologous stem cell transplantation provided both pain relief and stopped the progression of osteonecrosis of the femoral head in patients with sickle cell disease. The focus of MSC therapy in currently active clinical trials include: articular cartilage resurfacing with MSCs in osteoarthritis, non-union of fractures, periodontal disease, and spinal fusion.

Blood vessels

Studies have demonstrated a strong correlation between clinical risk factors for cardiovascular disease and EPC function and quantities. Disease states such as diabetes, coronary artery disease, smoking, and hypercholesterolemia are known to affect EPCs adversely, prompting efforts to improve clinical outcomes through EPC augmentation.²⁰⁰ Direct injection of EPCs, as well as growth factors, such as granulocyte-macrophage colony-stimulating factor have been used with some success following cardiac ischemia. A

meta-analysis found that intracoronary bone marrow cell infusion is a safe way to administer EPCs and is associated with a minor improvement in left ventricular function at 3–6 months following acute myocardial infarction.²⁰¹

Muscle

Satellite cells have generally been incompatible with systemic administration and exhibit poor viability and migration when delivered intramuscularly. Thus, the therapeutic potential of muscle stem cells has focused more on progenitor populations derived from the endothelial lineage. These cells, which include mesoangioblasts, pericytes, and CD133+ cells, have significant myogenic potential and readily cross the endothelium, making intra-arterial delivery possible.¹⁸⁵ In animal models, these muscle progenitors have shown the ability to restore muscle function and to reconstitute the satellite stem cell compartment to varying degrees.²⁰² Numerous human trials for Duchenne muscular dystrophy demonstrated effective dystrophin production with the use of injected stem cells, but clinical benefits have not been observed.²⁰³ Clinical trials have also been conducted with muscle stem cells for ischemic heart disease and stress urinary incontinence, with mixed improvements in muscle function.²⁰⁴

Nervous system

Treating disorders of the central nervous system (CNS) has been one of the most challenging areas of modern medicine. Regenerative medicine using defined stem and progenitor cells offers the potential for neuroprotection (to prevent further cell loss) and/or neuronal replacement (to replace damaged or lost neurons). Both of these strategies can be envisioned in chronic neurodegeneration (i.e. age-related macular degeneration and Alzheimer's disease) and genetic neurodegeneration, as well as in injuries to the CNS (spinal cord injury, stroke, and traumatic brain injury).

A seminal finding in advancing regenerative medicine for neurological disorders was the demonstration that neurogenesis continues to occur in the adult human brain.²⁰⁵ This discovery, together with the identification and expansion of human neural stem cells,^{206,207} has led to a plethora of studies investigating neuroregeneration.^{206,208} One such human neural stem cell population is the HuCNS-SC, an adult tissue-specific stem cell, first characterized in 2000 by Stem Cells, Inc.^{209,210} Each HuCNS-SC bank is created from purified neural stem cells from a single fetal brain tissue at 16–20 weeks' gestation by prospective isolation using flow cytometry.²⁰⁶ Manufactured under cGMP standards, the company's HuCNS-SCs are purified, expanded in culture, cryopreserved, and then stored as banks of cells, ready to be made into individual patient doses when needed. Building on the promising animal studies,²¹¹ where evidence of engraftment, global CNS migration and multi-lineage differentiation (astrocytes, oligodendrocytes, and neurons) was demonstrated, these allogeneic cells were then tested in phase I/II clinical trials for specific CNS disorders based on neuroprotective and neuronal replacement strategies to determine safety and preliminary efficacy of HuCNS-SCs.^{206,212} As HuCNS-SCs have now been shown to engraft and survive long term,^{209,213} there is possibility of a durable clinical effect following single transplantation. In the multi-center study of spinal cord injury, seven patients received cell transplantation above and below the site of injury. In

addition to safety, 12-month data analysis also revealed sustained improvements in sensory function that emerged consistently around three months after transplantation and persisted until the end of the study. The patterns of sensory gains were confirmed to involve multiple sensory pathways and were observed more frequently in the patients with less severe injury. HuCNS-SCs were also shown to be safe and effective in the treatment of congenital neurodegenerative diseases.^{206,212} Further investigation is now underway with larger patient numbers, to build upon promising phase I/II clinical data.

Prospective clinical applications of stem cell therapy

Scaffolds for stem cell delivery

Stem cells exist in tightly controlled environmental niches and alterations in this microenvironment can dramatically modify their behavior and capabilities. Furthermore, they are often utilized in the setting of disease or injury where toxic signals that can impair their function are prevalent. Thus, strategies using biomaterial scaffolds are important to stem cell therapy as they help provide a controlled environment in which implanted cells can be protected from harmful stimuli. Biomaterial matrices can also be used to deliver genetic material and/or inductive biochemical cues, which allow for some degree of developmental control over the delivered stem cells (Fig. 12.22). In terms of tissue and organ regeneration, scaffolds provide the structural template on which to build new tissues and can thus be prefabricated based on their ultimate purpose. For example, more rigid scaffolds are much better

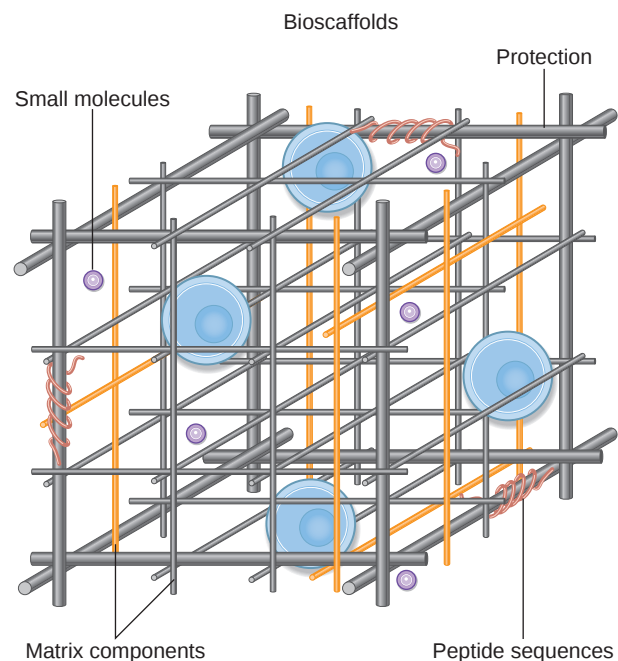


Fig. 12.22 Bioscaffold construct. Bioscaffolds can be tailored based on the stem cell type and small molecule utilized, as well as the protein type, peptide sequence, and matrix components.

suited for bone engineering, whereas soft flexible scaffolds are ideal for skin applications.

Scaffolds can be broadly separated into two categories: native or synthetic. Native scaffolds include those derived from living or cadaveric donors and can be autogenous, allogeneic, or xenogeneic. An excellent example of the utilization of such scaffolds is the treatment of massive burns with dermal substitutes derived from a wide range of human and nonhuman sources. Native matrices can be obtained through decellularization of tissues and whole organs. The matrices can then be seeded with exogenous therapeutic cells.^{214,215} These techniques include the use of physical/mechanical forces, chemicals, and enzymatic agents to remove cellular material with minimal disruption to the matrix.²¹⁶

Recently, there has been increased focus on “smart” biomaterials.²¹⁷ These materials incorporate peptide sequences capable of better mimicking the native cellular environment and can significantly modulate cell differentiation, adhesion, and proliferation.²¹⁸ Smart polymers may allow scaffolds to respond to temperature, pH, light, or ionic interactions with altered mechanical properties, hydrophobicity, collapse, or expansion.²¹⁹

Numerous studies have demonstrated the benefits of utilizing stem cell-scaffold constructs in regenerative medicine. For one, scaffolds provide a highly modifiable vehicle for inductive factors. Fang *et al.* utilized plasmid DNA loaded onto collagen sponges and demonstrated successful *in vivo* genetic manipulation of fibroblasts to induce bone formation in rats.²²⁰ In another study, poly(lactide-coglycolide) scaffolds loaded with DNA plasmid demonstrated enhanced cell transfection and matrix formation compared to naked plasmid injection alone.²²¹ Schek *et al.* found that bone formation was greater with hydrogel delivery of BMP-7-expressing adenovirus in mice compared to non-hydrogel controls.²²² While there are still considerable challenges facing the development of the ideal artificial scaffold, ongoing innovation has led to significant advances combining innovative scaffolding design with increased understanding of stem cell biology.²²³ Heightened awareness of the importance of scaffold topography and porosity, degradation rates, and incorporation of bioactive molecules has continued abreast of technological and stem cell advances.²²⁴ Three-dimensional printing strategies for scaffold manufacture have also accelerated personalized scaffold development, and one can envisage adaption of this computational technology to create effective personalized scaffolds for reconstructive surgery generated from 3D imaging in addition to scaffolds for stem cell delivery.^{223,224}

In summary, as researchers continue to unravel the complex signals and interactions that act to modulate stem cell behavior, advances in biomaterial techniques will be crucial to our ability to recapitulate with accuracy the various endogenous stem cell microenvironments.²¹⁷

Genetic induction therapies

Cell-based regenerative strategies are also critically dependent on the biochemical signaling environment. Exogenous administration of specific growth factors and cytokines can induce stem cell differentiation, which provides researchers with a powerful means of manipulating stem cell behavior

in vitro. Stem cells can also be coaxed down various paths of differentiation through gene transfer and cytokine therapies (Fig. 12.23). However, in order for these inductive modalities to be used effectively *in vivo*, they must be delivered in an appropriately controlled spatiotemporal manner over the timescales necessary to complete stem cell repair and tissue regeneration.

Stem cell-directed gene therapy has demonstrated enormous potential following the cure of children with X-linked severe combined immune deficiency and adenosine deaminase deficiency.^{225,226} However, two of 10 children treated subsequently developed leukemia, significantly tempering enthusiasm for stem cell gene therapy. Another hurdle has been the lack of relevant *in vitro* and animal models to predict efficacy in humans.²²⁷ Lastly, common vector systems currently employed in gene therapy that utilize Moloney murine leukemia virus, human immunodeficiency virus, and lentivirus are far from ideal as concerns regarding adverse inflammatory responses to viral components are always present.

Gene transfer of growth factors such as insulin-like growth factor and FGF has improved wound healing in animal models.^{228,229} Recent studies have demonstrated that lentiviral vectors may be preferred for long-term transfection of skin cells whereas adenoviral or adeno-associated viruses may be better suited for short-term skin therapies.²³⁰ Margolis *et al.* used replication-incompetent adenovirus to express PDGF for chronic venous leg ulcers in a phase I clinical trial.²³¹ Non-viral gene therapies through liposomal gene transfer have also been effectively used for wound regeneration.²³²

Iwaguro *et al.* found that VEGF gene transfer could be used to augment EPC function for vascular regeneration,²³³ and demonstrated improved EPC adhesion, vascular incorporation, and proliferation in a rodent limb ischemia model. EPCs

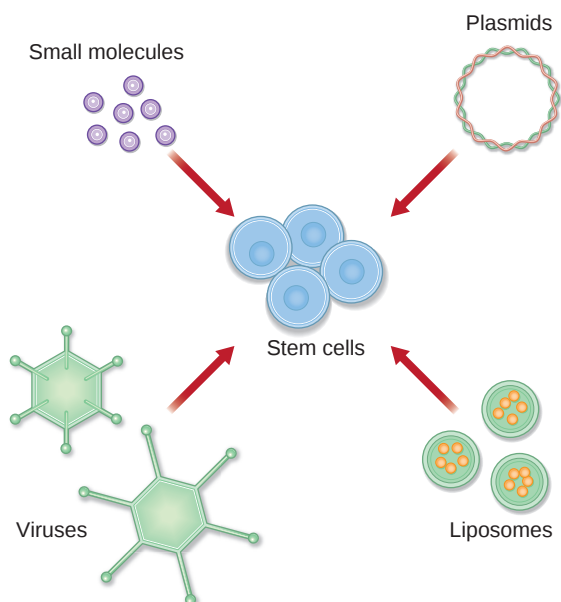


Fig. 12.23 Induction strategies for gene therapy. Small molecules, plasmids, or liposomes can stimulate stem cell differentiation.

have been transfected to produce anticoagulant proteins in an angioplasty injury model²³⁴ and VEGF-transfected EPCs have been used to fabricate bioengineered vascular grafts.²³⁵ Gene therapy of EPCs has included potential cancer therapy given their avid recruitment to neovascularizing areas.²³⁶

Stem cell-mediated gene therapy has also been proposed for a wide range of neurologic diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and neuropathic pain.²³⁷ For the treatment of nerve injury, Schwann cells have been transduced to express ciliary neurotrophic factor to augment nerve growth in rats.²³⁸ An adenoviral gene transfer system has also been developed for Schwann cell transfection and peripheral nerve injury.²³⁹ Thus, vector-mediated strategies provide another regenerative tool to control the genetic programming of delivered stem cells with the promise of replacing missing or dysfunctional organs.

iPS cells

Definitions

Pluripotency is the ability of a cell to differentiate into all cell types in the body. Originally thought to be a property unique to the blastocyst or inner cell mass of the early mammalian embryo, this tenet was challenged by a groundbreaking 2007 study published by Yamanaka *et al.* In this paper scientists definitively established a process of reprogramming or "inducing" pluripotency in a mature cell using a few key transcription factors in the cell (Fig. 12.24).²⁴⁰ The resulting cells have been named "induced" pluripotent stem cells as they have stem cell-like properties and can differentiate into all cell types found in the body.

The original conditions for creating iPS cells used a set of four transcription factors: Oct4, Sox2, Klf4, and c-Myc (Fig. 12.25) to revert mature cells into a more primitive stage and induce pluripotency. Since these original studies, scientists have refined the process and are now able to reprogram mature

cells with only two factors. Dr. Yamanaka, who described the original iPS cell, used a stochastic model to illustrate the mechanism behind this type of differentiation. In a stochastic model, most or all differentiated cells have the potential to become iPS cells with the use of four transcription factors. The idea is that a cell represents a "ball rolling down an epigenetic landscape from the totipotent state, going through the pluripotent state and rolling down a lineage committed state". With the development of normal adult cells, pluripotent cells appear briefly and cannot be stopped "on the slope." In contrast, ESCs are blocked by a "bump or roadblock formed by their epigenetic status". Thus, the four Yamanaka factors function to roll cells back to a pluripotent state.²⁴¹

iPS cells have a number of advantages over embryonic stem cells for use in regenerative medicine. Firstly, the use of iPS cells avoids the ethical conflicts associated with ESC derivation as iPS cells are generated from adult tissues. Secondly, since these cells can be harvested noninvasively for autologous re-implantation, they can bypass the immune rejection that limits the use of allogeneic cells. Thirdly, iPS cells can be derived from many different cell types. Early descriptions of iPS derivation used skin fibroblasts,^{242,243} which required only a small skin biopsy followed by 3–4 weeks of *in vitro* expansion. One major disadvantage of skin fibroblasts, however, is that they have a very low reprogramming efficiency (under 0.01%) when using the four Yamanaka factors and even lower without c-Myc. Furthermore, the length of transfection is an additional 3–4 weeks' time before ESC-like iPS cells begin to appear.²⁴⁴ Based on the epigenetic landscape model, fibroblasts are terminally differentiated and thus take a greater amount of time and energy to reprogram.

Keratinocytes from human foreskin biopsies and hair have also been used to generate iPS cells.²⁴⁵ These cells are similarly easy to harvest but also require an extended time for *in vitro* expansion. Compared to fibroblasts, keratinocytes derived from neonatal/juvenile foreskin have an approximate 100-fold increase in reprogramming efficiency. This has not, however, been seen with adult keratinocytes.

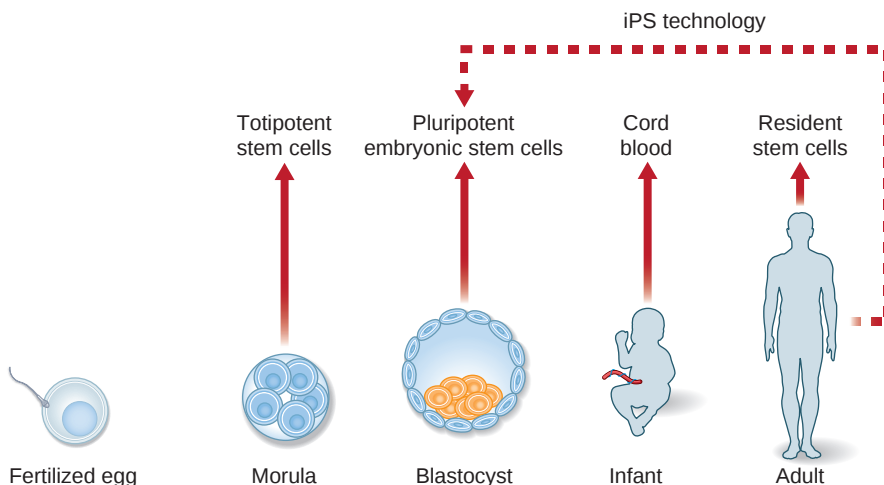


Fig. 12.24 Stem cells can be obtained during the different developmental stages of life. With the development of induced pluripotent stem cell (iPS) technology, adult cells can now be reprogrammed to become embryonic "stem cell-like" cells.

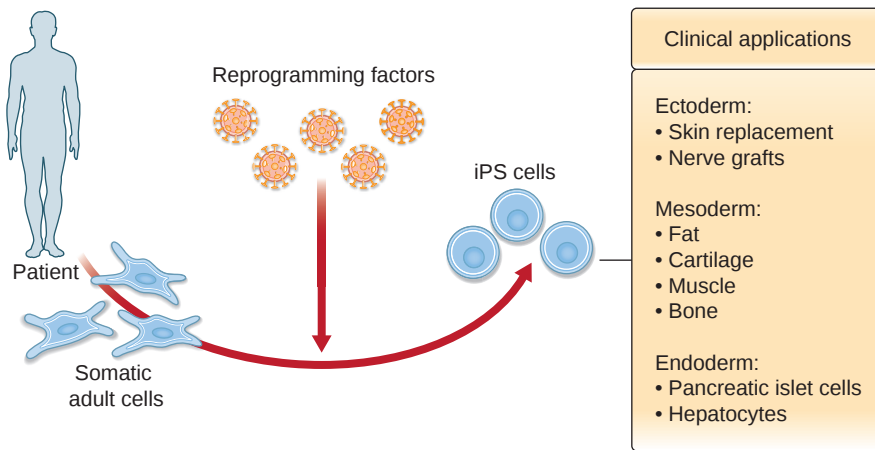


Fig. 12.25 By activation of four transcription factors, adult somatic cells can be reprogrammed into induced pluripotent stem cells, which then can differentiate into all the embryonic lineages: ectoderm, mesoderm, and endoderm.

Melanocytes have also been used to generate iPS cells. This is described by Utikal *et al.* in a 2009 paper, which sought to generate iPS cells more effectively by identifying somatic cell populations that could be reprogrammed with greater efficiency.²⁴⁶ Melanocytes inherently express high levels of Sox2 and thus can be reprogrammed with only three factors (Oct4, Klf4, and c-Myc). Original studies using all four Yamanaka factors demonstrated a five-fold higher reprogramming efficiency than seen with fibroblasts. In addition, the melanocytes could be reprogrammed in only 10 days.

Two laboratories have also described iPS cell derivation from cryopreserved umbilical cord blood cells. One laboratory was able to reprogram these cord blood cells successfully using only Oct4 and Sox2.²⁴⁷ A benefit of this technique is that cord blood can be stored for over 5 years and still retain the ability to be reprogrammed.

An even more abundant source of cells for iPS applications is human adipose tissue.²⁴⁸ Our laboratory has isolated adipose cells from lipoaspirates of adult patients and successfully reprogrammed the cells using the four Yamanaka factors. Small-volume liposuction, in a minimally invasive outpatient setting, allows for the harvest of millions of cells. It is estimated that 10 mL of fresh lipoaspirate yields 1 million cells after 48 hours of *in vitro* culture. This allows for immediate reprogramming without prior *in vitro* expansion. Even in slender patients, as little as 15–50 mL of fat can be used to derive iPS cells. Similarly, due to their rapid expansion, hASCs can be reprogrammed with a 20-fold greater efficiency than fibroblasts. Klf4 and c-Myc expression are high in these cells compared to fibroblasts and these cells do not require mouse feeder cells. This ease of harvest and speed of expansion and reprogramming make hASCs an exciting option for scientists exploring translational iPS strategies.²⁴⁸

Despite the excitement generated around iPS cells, methods for their derivation and use need to be further tested and improved. The use of lentiviruses and retroviruses lead to genomic integration of transgenes, which the host cells may not be able to silence completely. Furthermore, both Klf4 and c-Myc, factors commonly used to reprogram cells, are oncogenes. Future directions may involve using small molecules and interfering RNAs, or microRNAs to make iPS cell generation safer. With regard to cell culture, iPS cells still depend on a layer of inactivated MEFs. A Matrigel-coated surface could potentially allow for a feeder-free environment.

More recently, laboratories have found ways to circumvent the use of viruses by generating a non-viral minicircle vector to induce iPS formation.²⁴⁹ Minicircle vectors are supercoiled DNA molecules composed of a eukaryotic expression cassette. Minicircles also offer the advantages of having a higher transfection efficiency and longer ectopic expression due to low activation of exogenous silencing mechanisms. Reprogramming was successfully performed using hASCs from 3 different patients, making it an attractive option if rapid cell expansion and reprogramming are required.²⁴⁹

In 2007, a human sickle-cell anemia mouse model was successfully treated with genetically corrected hematopoietic progenitors generated from iPS cells.²⁵⁰ In spite of promising early successes such as this, however, a number of barriers had to be overcome prior to progression of iPS cell-based therapy to clinical use. For instance, the oncogenic transgene integration and mutagenesis involved in iPS cell reprogramming could induce cancer (Fig. 12.26). Virus-free generated iPS cells offer a potential solution.

Also, significant safety studies are required to determine the minimal number of undifferentiated iPS cells that can become a teratoma as current subcutaneous injection of iPS cells has gone on to generate teratomas. This suggests that iPS cells will likely need to be differentiated *in situ* prior to implantation to allow for appropriate tissue regeneration (Fig. 12.27). Lastly, from a commercialization standpoint, it has yet to be determined if a viable business model for patient-specific iPS treatments is possible given the safety considerations, as well as the challenge of their reprogramming.²⁴⁴

In vitro

Culture and maintenance of iPS cells

IMR90 human fibroblasts or other cell types to be reprogrammed can be maintained with DMEM containing 10% FBS, L-glutamine, 4.5 g/dL glucose, 100 U/mL penicillin, and 100 µg/mL streptomycin. All cells used for reprogramming should be passage two or less. Derived iPS cells can be maintained either on MEF feeder layer or on Matrigel-coated tissue culture dishes (ES qualified; BD Biosciences) with mTESR-1 hES Growth Medium (Stemcell Technology).²⁴⁸

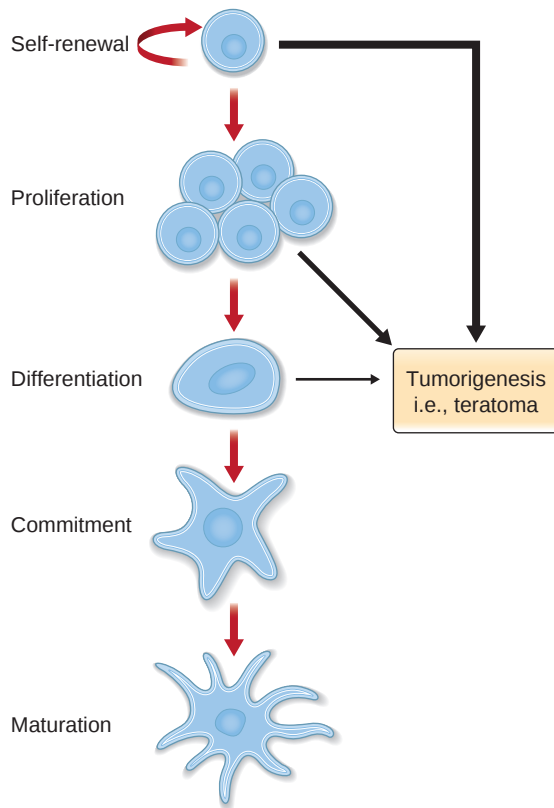


Fig. 12.26 One potential risk of using a multipotent self-renewing cell is the uncontrolled division of these cells leading to tumor formation. However, usually in tissue engineering a paucity of tissue, rather than excess, is the problem.

Lentivirus production and transduction

293FT cells (Invitrogen) are plated at ~80% confluence per 100-mm dish and transfected with 12 μ g each of lentiviral vectors (Oct4, Sox2, Klf4, c-Myc) plus 8 μ g packaging plasmids and 4 μ g VSVG plasmids using Lipofectamine 2000 (Invitrogen) following the manufacturer's instructions. The resulting supernatant should be collected 48 hours after transfection, filtered through a 0.45- μ m pore size cellulose acetate filter (Whatman), and mixed with PEG-it Virus Concentration Solution (System Biosciences) overnight at 4°C. Viruses are precipitated at 1500 g the next day and resuspended with Opti-MEM medium (Invitrogen).

In vitro differentiation

iPS cells cultured on Matrigel are treated with collagenase type IV (Invitrogen) and transferred to ultra-low attachment plates (Corning Life Sciences) in a suspension culture for 8 days with DMEM/F12 (1:1) containing 20% knockout serum (Invitrogen), 4.5 g/dL glucose, L-glutamine, 1% nonessential amino acids, 0.1 mM 2-mercaptoethanol, 50 U/mL penicillin, and 50 μ g/mL streptomycin to allow formation of embryoid bodies (EBs).

The EBs are then seeded in 0.25% gelatin-coated tissue culture dishes for another 3–8 days. Spontaneous differentiation of iPS cells into cells of mesoderm and endoderm lineages can be detected with appropriate markers by immunofluorescence. For osteogenic differentiation, similar osteogenic medium with ascorbic acid, and β -glycerol phosphate have been used along with supplementation of retinoic acid and bone morphogenetic proteins. Furthermore, there remains some dispute as to whether the EB formation step is necessary

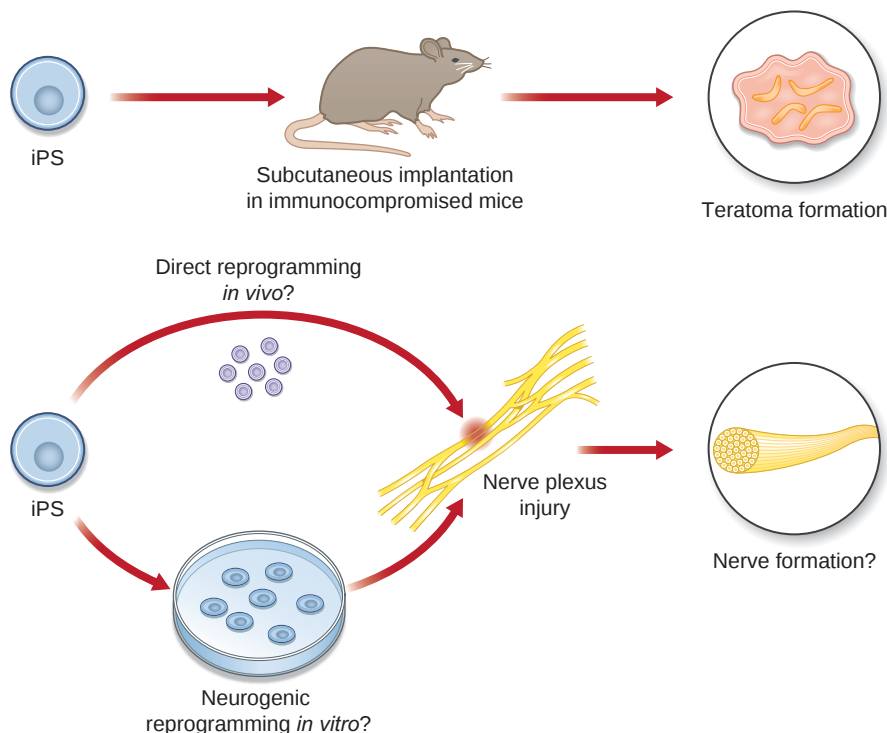


Fig. 12.27 When induced pluripotent stem cells (iPS) are placed subcutaneously, there is differentiation into all three embryonic lineages, resulting in the formation of a teratoma. The hope is that these cells can be reprogrammed prior to implantation or *in situ* to repair tissues that cannot be repaired with human adipose-derived stromal cells such as neural tissues.

and leads to more efficient osteogenic differentiation or whether omission of this step is possible. Differentiation into dopaminergic neurons can be performed using a co-culture of hASC iPS cells with PA6 cells.

***In vivo* models and potential clinical correlates**

The use of iPS technology can potentially revolutionize the field of tissue engineering by allowing the creation of any cell type from mature cells harvested via noninvasive methods. We believe that the derivation of iPS cells from hASCs holds several advantages compared to other cell types such as neural stem cells, liver cells, and skin fibroblasts. First, the lipoaspiration procedure for isolating hASCs is relatively simple, fast, and safe. Second, it is easy to obtain a large quantity of hASCs as the starting population for reprogramming after a single lipoaspiration operation. Millions of hASCs can be derived on the same day of lipoaspiration, and the reprogramming can be performed immediately. Up until recently, iPS cells required a layer of mouse fibroblasts to survive in an undifferentiated state, which raised concerns for potential contamination of the cultured human cells by mouse proteins and subsequent rejection by human recipients following transplantation. Feeder-free derivation of iPS cells from hASCs thus represents a more clinically applicable method for derivation of iPS cells and should enable more efficient and rapid generation of patient-specific and disease-specific iPS cells.²⁴⁸

Though the first clinical trial utilizing iPS cells is currently underway in Japan, therapeutic utilization and delivery of iPS cells still requires further refinement. Treatment of a focal deficit such as those present in spinal cord injuries, Parkinson's disease or type I diabetes might involve direct delivery. More systemic diseases such as muscular dystrophies, however, might require multiple intravenous injections for systemic delivery.²⁵¹ The use of animal models can enable scientists to address these and other concerns about safety and efficacy prior to use in humans.

Thus, three main hurdles exist for iPS utilization to become mainstream:

1. Animal proteins are still commonly used during the reprogramming of human cells in the form of a mouse fibroblast feeder layer. A solution would be widespread use of a feeder-free layer or Matrigel without animal components.
2. Currently viruses used for reprogramming can integrate into the genome and cause mutations and possible malignancy. What is needed is a robust and efficient non-viral approach such as the minicircle plasmid for reprogramming.
3. *In vivo*, undifferentiated iPS cells form teratomas. Direct differentiation of iPS cells to the differentiated cells of interest prior to placement *in vivo* may alleviate this concern.

While these hurdles are being addressed, an area of great interest in the realm of iPS cells is that of disease modeling.²⁵² iPS cell technology has provided previously unanticipated possibilities to model rare human diseases *in vitro*.²⁵² Reprogramming somatic cells from affected patients into an embryonic stem cell-like state followed by differentiation into cell types relevant to human disease generates an unlimited source of human tissue carrying the genetic variations that instigated or facilitated disease development. In addition, recently developed gene editing technologies enable the targeted modification of human cells for gene disruptions, genetic repair, or insertion of reporter genes.^{252,253} The ability to modify single base pairs, thereby seamlessly correcting or introducing disease-causing mutations in human pluripotent stem cells, allows the creation of genetically controlled experimental model systems in which the disease-causing genetic variation is the sole experimental variable.²⁵⁴⁻²⁵⁶ This strategy could substantially simplify the analysis of the interaction between these genomic variants and disease phenotypes, thereby revealing new insights into the pathophysiology of monogenic and complex diseases.²⁵²



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Wound healing

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SYNOPSIS

- There are three general techniques of wound treatment: primary intention, secondary intention, and tertiary intention
- The following overlapping phases drive the overall healing response: hemostasis, inflammation, proliferation, and remodeling
- Successful hemostasis or blood coagulation results in prevention of blood loss by plugging the wound within seconds through vasoconstriction and formation of a hemostatic blood clot consisting of platelets and fibrin. The process is divided into initiation and amplification. Initiation is caused by an extrinsic pathway, whereas amplification is executed by an intrinsic pathway
- The inflammatory response during normal healing is characterized by spatially and temporally changing patterns of specific leukocyte subsets. Dysregulated inflammation complicates wound healing. Complete resolution of an acute inflammatory response is the ideal outcome following an insult
- Infection is a common problem in chronic wounds, frequently resulting in nonhealing wounds and significant patient morbidity and mortality. Microorganisms do not always live as pure cultures of dispersed single cells but instead accumulate at interfaces to form polymicrobial aggregates such as films, mats, flocs, sludge, or biofilms
- In an open wound that has undergone contraction, restoration of an intact epidermal barrier is enabled through wound epithelialization, also known as re-epithelialization. During the proliferative phase of wound healing, the granulation tissue is light red or dark pink in color because of perfusion by new capillary loops. It is soft to the touch, moist, and granular in appearance. The granulation tissue serves as a bed for tissue repair.
- Wound healing endpoint determination should include a combination of visual inspection and measurements of skin barrier function such as transepidermal water loss (TEWL) for accurate determination of closure.
- Wound vascularization may be achieved by angiogenesis or vasculogenesis
- A wound is generally considered chronic if it has not healed in 4 weeks. Chronic wounds can be broadly classified into three major categories: venous and arterial ulcers, diabetic ulcers, and pressure ulcers
- Vascular complications commonly associated with problematic wounds are primarily responsible for wound ischemia. Limitations in the ability of the vasculature to deliver O₂-rich blood to the wound tissue leads to, among other consequences, hypoxia. Three major factors may contribute to wound tissue hypoxia: (1) peripheral vascular diseases garroting O₂ supply; (2) increased O₂ demand of the healing tissue; and (3) generation of reactive oxygen species (ROS) by way of respiratory burst and for redox signaling
- Small RNAs are a new class of regulators of eukaryotic biology. Alongside other small interfering RNAs (siRNAs), microRNAs (miRNAs) execute post-transcriptional gene silencing through mRNA destabilization as well as translational repression. miRNAs are emerging as a key regulator of the overall wound-healing process
- The regenerative potential of injured adult tissue suggests the physiological existence of cells capable of participating in the reparative process. Bone marrow-derived mesenchymal stem cells (BM-MSCs) have been shown to promote the healing of diabetic wounds, implying a profound therapeutic potential for skin defects such as chronic wounds and burns

Introduction

Physical trauma represents one of the most primitive challenges that threatened survival. In other words, injury eliminated the unfit. A Sumerian clay tablet (c. 2150 BC) described early wound care that included washing the wound in beer and hot water, using poultices from substances such as wine dregs and lizard dung, and bandaging the wound. Ancient scriptures depicting the science of life or *Ayurveda* date from the sixth to seventh century BC, and represent the beginning of planned physical injury with the intent to cure.^{1,2} Hippocrates (c. 400 BC) detailed the importance of draining pus from the wound, and Galen (c. 130–200 AD) described the principle of first- and second-intention healing.³ Wound healing advanced slowly over the centuries, with major advances in the 19th century in the importance of controlling infection, hemostasis, and necrotic tissue.⁴ Today, surgical trauma, taken together with injury caused during accidents

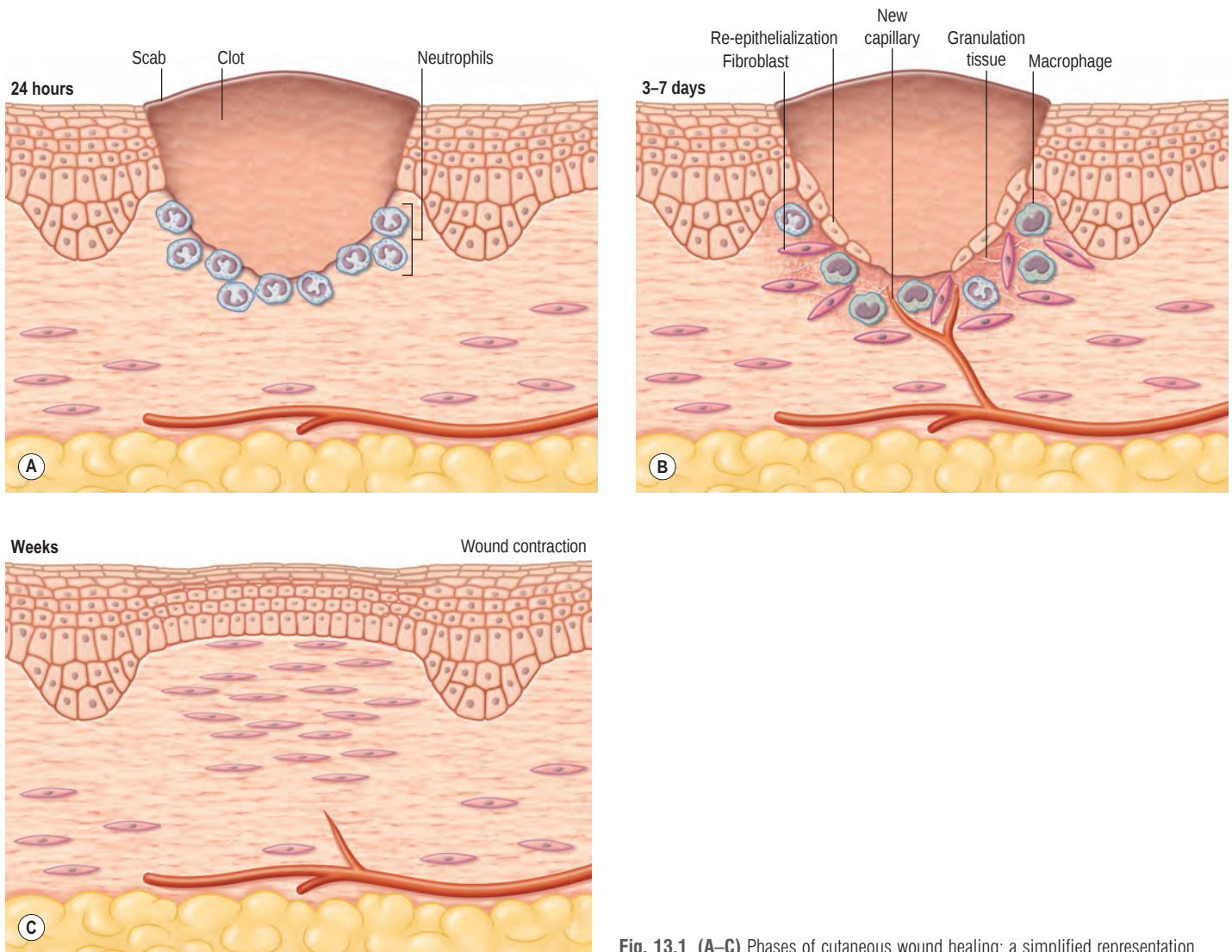


Fig. 13.1 (A–C) Phases of cutaneous wound healing: a simplified representation.

and secondary to other clinical conditions, e.g., diabetes, represents a substantial cost to society.⁵ Any solution to wound-healing problems will require a multifaceted comprehensive approach. First and foremost, the wound environment will have to be made receptive to therapies. Second, the appropriate therapeutic regimen needs to be identified and provided while managing systemic limitations that could secondarily limit the healing response. This chapter aims to present an overall outline of the cutaneous wound-healing process.

The wound-healing process

The entire wound-healing process may be viewed as a cascade that is governed by numerous feedback and feed-forward regulatory loops driven by signals from the wound tissue itself, wound microenvironment, as well as interventions under conditions where the wound is subjected to therapy. To understand the several interdigitated biological processes that drive the overall healing response, wound healing is commonly discussed as the following overlapping phases: hemostasis and inflammation, proliferation (granulation,

vascularization, and wound closure; closure may be discussed as wound contraction and epithelialization) and remodeling (continues from weeks to years and encompasses collagen deposition, acquisition of wound tensile strength, and turnover of extracellular matrix (ECM) components). These stages, taken as a whole, are also referred to as the wound-healing cascade (Fig. 13.1).

Hemostasis

For bleeding wounds, the highest priority is to stop bleeding and this is achieved by hemostasis. Hemostasis is thus a protective physiological response to vascular injury that results in exposure of blood components to the sub-endothelial layers of the vessel wall. Through successful hemostasis blood loss is prevented by plugging the wound within seconds through vasoconstriction and formation of a hemostatic blood clot consisting of platelets and fibrin. Hemostasis requires both platelets and the blood coagulation system. The process of blood coagulation may be subdivided into initiation and amplification. Initiation is caused by an extrinsic pathway, whereas amplification is executed by an intrinsic pathway.

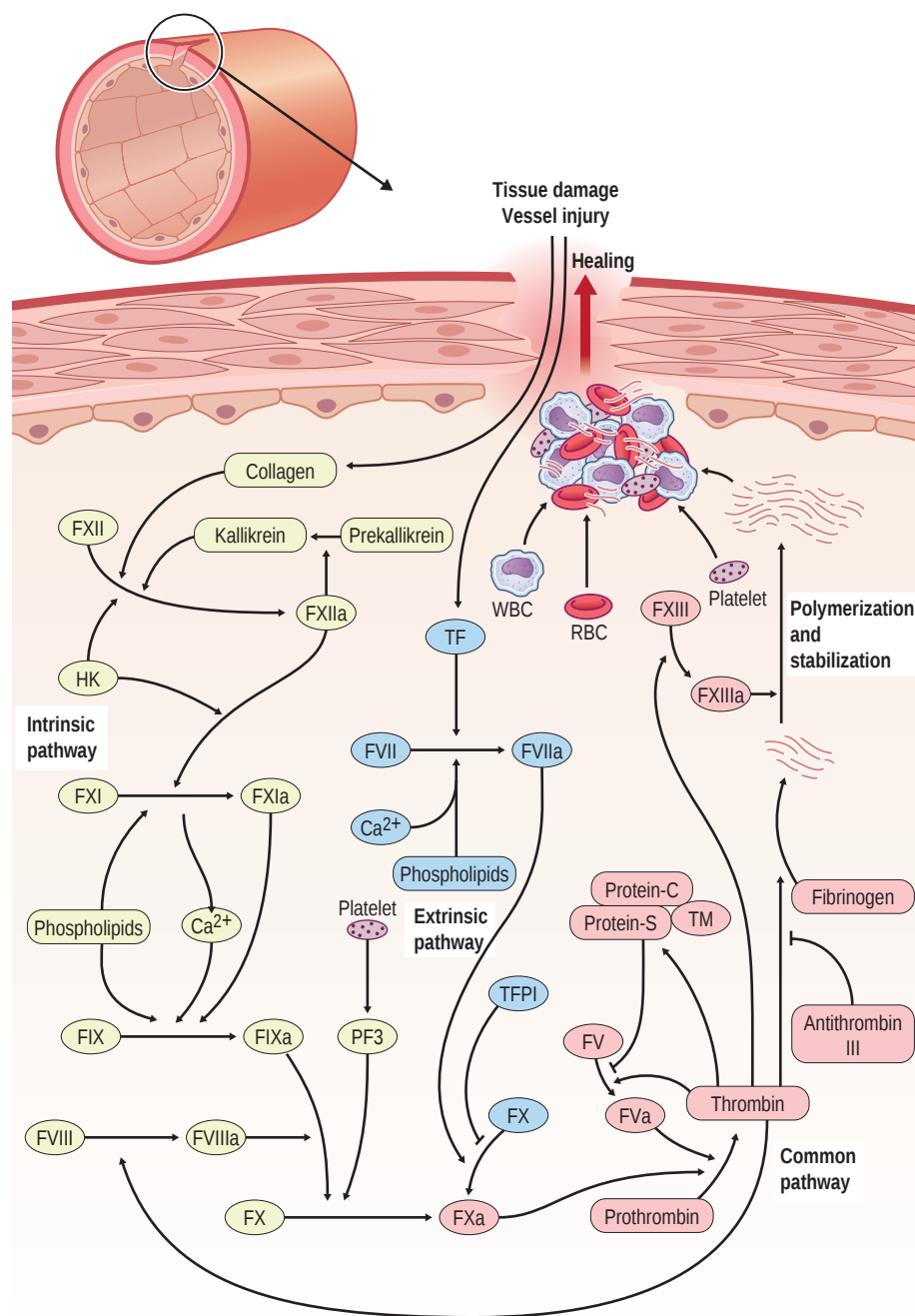


Fig. 13.2 The blood clotting cascade. FXII, factor XII, HK, high-molecular-weight kininogen; PF3, platelet factor 3; RBC, red blood cell; TF, tissue factor; TFPI, tissue factor pathway inhibitor; TM, thrombomodulin; WBC, white blood cell.

The intrinsic pathway consists of plasma factor XI (FXI), IX, and VIII (Fig. 13.2). Tissue factor (TF) generates a “thrombin burst”, a process by which thrombin is released instantaneously. Thrombin is a key driver of the overall coagulation cascade.

The extrinsic pathway responsible for the initiation of blood coagulation consists of the transmembrane receptor TF and plasma FVII or VIIa. On the other hand, the intrinsic pathway consists of plasma FXI, FIX, and FVIII. Under physiological conditions, TF is constitutively expressed by adventitial cells surrounding blood vessels and initiates clotting. Examples of such adventitial cells include vascular smooth-muscle cells, pericytes, and adventitial fibroblasts.^{6,7} TF may

also contribute to amplification of blood coagulation through its so-called blood-borne form, which is present as cell-derived microparticles as well as through TF expressed within platelets.⁶⁻⁸

Levels of FVIIa, a key player of the extrinsic pathway, in the circulating blood are higher than any other activated coagulation factor. Following injury to the blood vessel wall, FVII comes into contact with TF expressed on TF-bearing cells (e.g., white blood cells) and forms an activated complex (TF-FVIIa). TF-FVIIa activates FIX and FX, resulting in FIXa and FXa, respectively. FVII is activated by thrombin, FXIa, FXII, and FXa. The activation of FXa by TF-FVIIa is almost immediately inhibited by the TF pathway inhibitor. FXa and

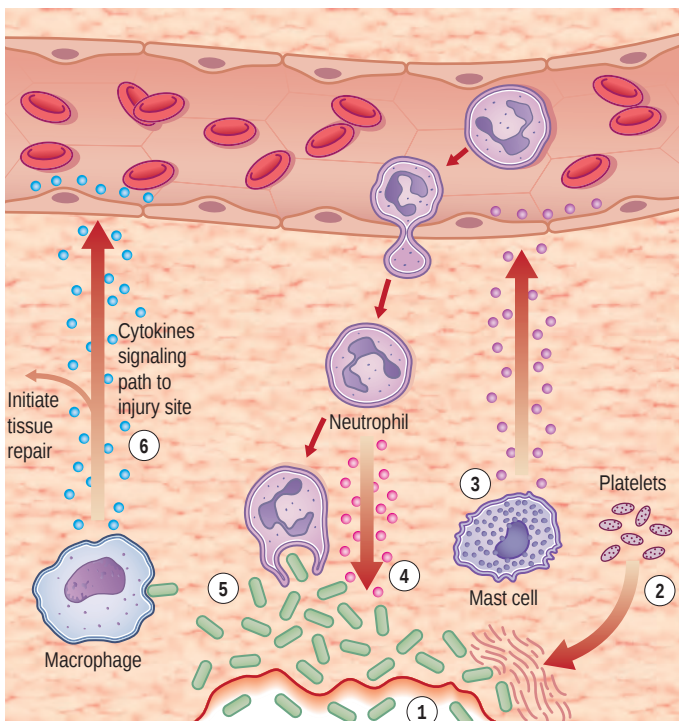
its cofactor FVa form the prothrombinase complex, which activates prothrombin to thrombin. Thrombin is a serine protease that plays a central role in hemostasis after tissue injury by converting soluble plasma fibrinogen into an insoluble fibrin clot and by promoting platelet aggregation. Thrombin activates other components of the coagulation cascade, including FV and FVIII, which in turn activates FIX and cascades to the activation of FX. Thrombin also activates and releases FVIII from being bound to von Willebrand factor. FVIIIa is the cofactor of FIXa, and together they form the “tenase” complex, which activates FX. In this way the cycle continues. The intrinsic pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen, prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein, and FXII becomes FXIIa. FXIIa converts FXI into FXIa. FXIa activates FIX, which together with its cofactor FVIIIa forms the tenase complex. The tenase complex activates FX to FXa (see Fig. 13.2).

The blood clot physically helps plug the wound, minimizing blood loss. It is primarily made up of cross-linked fibrin, cells such as erythrocytes and platelets, as well as other ECM proteins such as fibronectin, vitronectin, and

thrombospondin. Current understanding portrays the clot as a dynamic structural matrix containing functionally active proteins and cells. In addition to containment of blood loss, the clot serves as a first aid against microbial invasion. The clot also serves as a provisional matrix for the homing of blood-borne cells, including inflammatory as well as stem or progenitor cells. The provisional matrix is enriched in cytokines and growth factors which then regulate the function of the homing cells.^{9,10}

The formation of blood clot is initiated by the proteolytic cleavage of fibrinogen by thrombin. As a result, fibrin is produced and forms cross-links with each other. Cross-linked fibrin entraps platelets, and together they adhere to the sub-endothelium through adhesion molecules called integrins. Clot fibrin plays a key role in mounting the inflammatory process as well as in facilitating wound angiogenesis and stromal cell proliferation. Fibrin binds to integrin CD11b/CD18 on infiltrating monocytes and neutrophils. It also binds to fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF) that help the wound tissue vascularize. Fibrin also binds to insulin-like growth factor-I and promotes stromal cell proliferation.^{11,12}

A blood clot represents the seat of wound chemotaxis. Thrombin, released by platelets at the wound site, is an early mediator of clot development.¹³ Thrombin is a serine protease that converts soluble plasma fibrinogen into an insoluble fibrin clot. In addition, it promotes platelet aggregation. Thrombin function may be viewed as an interface between the hemostasis phase of wound healing and the ensuing inflammatory phase as it plays a potent role in mounting wound inflammation. The proinflammatory effects of thrombin include stimulation of vasodilation responsible for plasma extravasation, edema, and an increased expression of endothelial cell adhesion molecules that helps monocytes and other cells extravasate and infiltrate the wound site. Thrombin also induces the release of proinflammatory cytokines like CCL2, interleukin-6 (IL-6), and IL-8 by endothelial cells. These cytokines induce monocyte chemotaxis.¹⁴ Furthermore, thrombin induces the release of inflammatory cytokines by monocytes, including IL-6, interferon- γ , IL-1 β , and tumor necrosis factor- α (TNF- α). These early-phase cytokines are typically proinflammatory, which may govern the differentiation of blood-derived monocytes into M1 wound macrophages.¹⁵ Wound chemotaxis is also driven by the degradation of fibrin and subsequent activation of the complement system. As part of this process, several chemotactic agents and cytokines are released, which in turn launch the inflammatory phase of wound healing through chemotactic recruitment of blood-borne immune cells (Fig. 13.3).¹⁶ Platelets are one of the earliest sources of cytokines which execute immune cell chemotaxis as well as macrophage activation. Once trapped in the fibrin net, platelets release granules that function as a reservoir for biologically active proteins, such as RANTES (regulated on activation, normal T cell expressed, and secreted or CCL5), thrombin, transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), and VEGF. CCL5 is one of the most potent monocyte chemoattractants released by platelets after injury. Other cytokines and chemokines that attract monocytes to the wound bed include monocyte chemoattractant protein-1 (MCP-1) (CCL2), MIP-1 α (CCL3), TGF- α , fibronectin, elastin, C5a, C3a, nerve growth factor, and ECM components.^{17,18}



- ① Bacteria and other pathogens enter wound.
- ② Platelets from blood release blood-clotting proteins at wound site.
- ③ Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma and cells to injured area.
- ④ Neutrophils and macrophages remove pathogens by phagocytosis.
- ⑤ Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.
- ⑥ Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

Fig. 13.3 The wound inflammatory response.

Inflammation

Tissue injury triggers an acute-phase inflammation (Latin, *inflammare*, to set on fire) response that is meant to prepare the wound site for subsequent wound closure (see Fig. 13.3). Inflammation encompasses a series of responses of vascularized tissues of the body to injury. Local chemical mediators that are biosynthesized during acute inflammation give rise to the macroscopic events characterized by Celsus in the first century, namely, *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). At cellular and molecular levels, inflammation results from the coordination of manifold systems of receptors and sensors that affect transcriptional and post-translational programs necessary for host defense and resolution of infection. During normal healing, the inflammatory response is characterized by spatially and temporally changing patterns of specific leukocyte subsets.

Platelets

Formation of the clot or thrombus is dependent on platelet activation. The platelet-rich blood clot also entraps polymorphonuclear leukocytes (neutrophils). This helps amplify blood coagulation and lays the foundation for the subsequent acute-phase inflammatory response. In a matter of hours after injury, large numbers of neutrophils extravasate by transmigrating across the endothelial cell wall of blood capillaries to the wound site. To enable this, local blood vessels are activated by proinflammatory cytokines such as IL-1 β , TNF- α , and interferon- γ . These cytokines induce the expression of adhesion molecules necessary for adhesion of leukocytes and diapedesis (Fig. 13.4). Adhesion molecules such as integrins as well as P-selectin and E-selectin play a central role in enabling diapedesis of neutrophils (Fig. 13.5). These adhesion molecules bind with integrins expressed on the cell surface of neutrophils, such as CD11a/CD18 (LFA), CD 11b/CD18 (MAC-1), CD11c/CD18 (gp150, 95), and CD11d/CD18. Alongside cytokines, chemokines play a major role in mounting acute-phase inflammation after injury. Chemokines include IL-8, MCP-1, and growth-related oncogene- α . In the case of an infected wound, bacterial products such as lipopolysaccharide and formyl-methionyl peptides can enhance neutrophil recruitment to the wound site (Fig. 13.6).

Neutrophils

Neutrophils traverse postcapillary venules at sites of inflammation, degrade pathogens within phagolysosomes, and undergo apoptosis. Neutrophils serve a wide range of functions, ranging from phagocytosis of infectious agents to cleansing of devitalized tissue. When coated with opsonins (generally complement and/or antibody), microorganisms bind to specific receptors on the surface of the phagocyte and invagination of the cell membrane occurs with the incorporation of the microorganism into an intracellular phagosome. There follows a burst of oxygen consumption, and much, if not all, of the extra oxygen consumed is converted to highly reactive oxygen species. This is called respiratory burst. In addition, the cytoplasmic granules discharge their contents into the phagosome, and death of the ingested microorganism soon follows. Among the antimicrobial systems formed in the

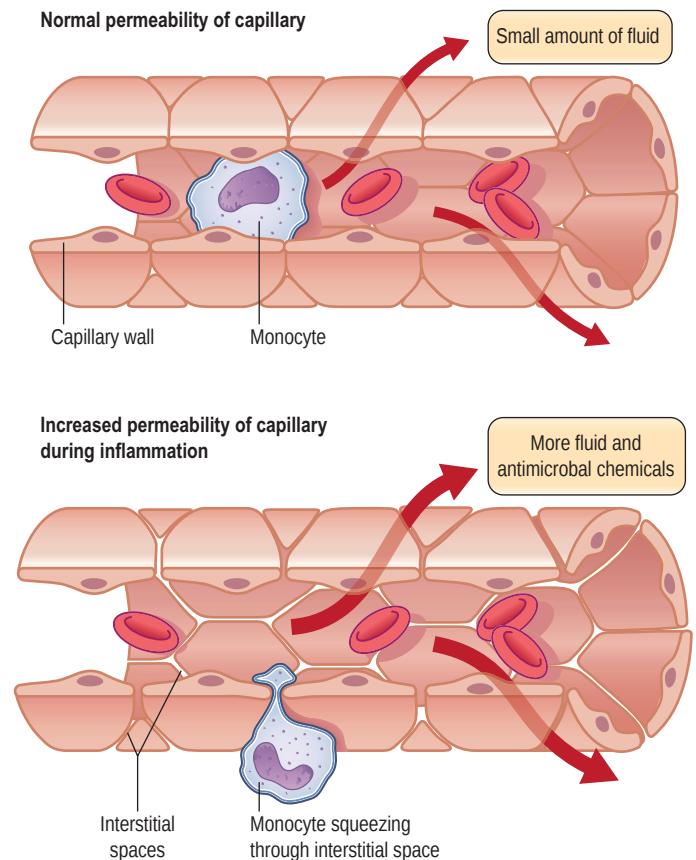


Fig. 13.4 Diapedesis. In healthy permeable capillaries the endothelium lining prevents blood cells from leaving the circulation. In response to injury, blood vessels around the wound site undergo vasodilation, increasing the permeability of capillaries. Such change enables inflammatory cells to extravasate through the capillary wall and migrate to the site of injury. This process includes release of fluid from the vessels to the extracellular space, resulting in the edematous response commonly noted during inflammation. Blood vessels possess a built-in pathway for such diapedesis to occur in response to tissue injury.

phagosome is one consisting of myeloperoxidase (MPO), released into the phagosome during the degranulation process, hydrogen peroxide (H_2O_2), formed by the respiratory burst and a halide, particularly chloride. The initial product of the MPO- H_2O_2 -chloride system is hypochlorous acid, and subsequent formation of chlorine, chloramines, hydroxyl radicals, singlet oxygen, and ozone has been proposed. These same toxic agents can be released to the outside of the cell, where they may attack normal tissue and thus contribute to the pathogenesis of disease.¹⁹ Other products delivered by neutrophils to the wound site include antimicrobials such as cationic peptides and eicosanoids as well as proteases such as elastase, cathepsin G, proteinase 3, and urokinase-type plasminogen activator. The balance of neutrophil-released protease levels and intrinsic inhibitors in the wound environment is important for wound healing progression.²⁰ Chronic non-healing wounds have elevated levels of neutrophil-derived proteases, specifically matrix metalloproteases (MMPs), indicating persistent neutrophil presence. The effects of MMPs are specifically inhibited by the enzymatic group known as tissue inhibitors of matrix metalloproteases (TIMPs) and these are present in abnormally low levels in chronic wounds. The imbalance between MMPs and TIMPs creates a hostile wound

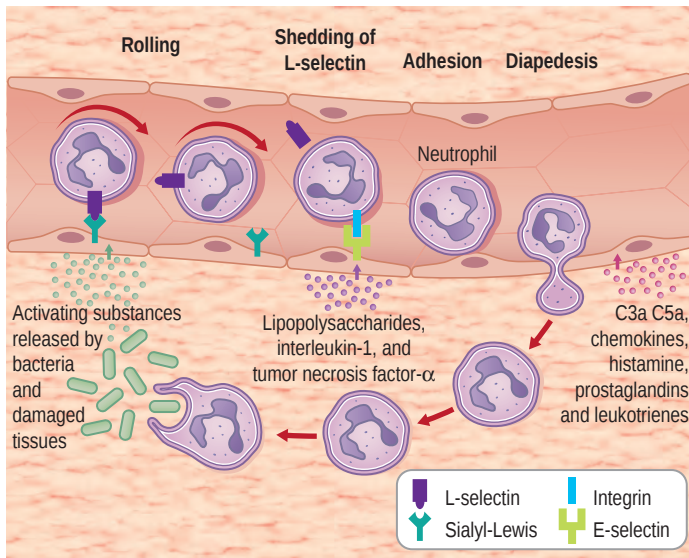


Fig. 13.5 Extravasation of neutrophils in response to tissue injury. Neutrophils move along the capillaries in a rolling motion which is facilitated by the binding and release of L-selectin on the neutrophil surface to sialyl-Lewis x, a carbohydrate ligand expressed on the inner wall of capillaries by endothelial cells. Upon injury and/or infection the release of lipopolysaccharides, tumor necrosis factor- α , and interleukin-1 results in the shedding of L-selectin by the neutrophils which then strongly adhere to the inner wall of the capillary by the binding of integrin on the neutrophils to E-selectins on endothelial cells. After such adhesion, the process of diapedesis begins, allowing the neutrophils to extravasate to the wound site.

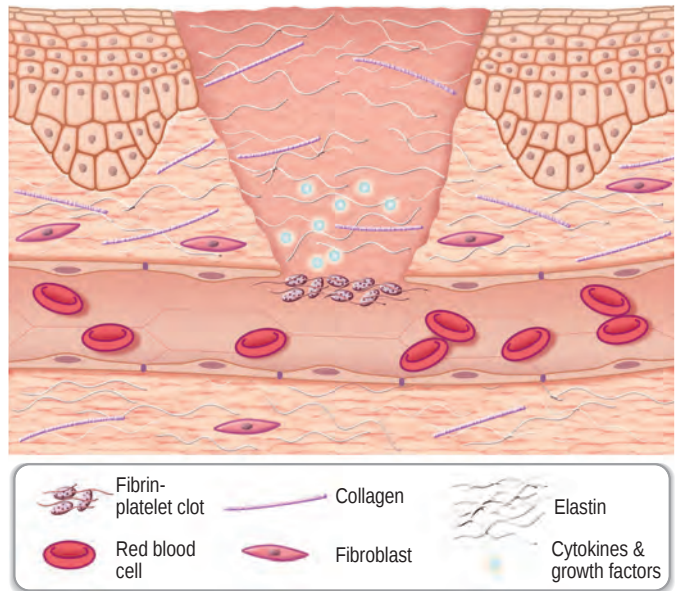


Fig. 13.6 Diapedesis and migration of leukocytes to the wound site.

environment as elevated protease levels result in tissue damage and inflammation that self-perpetuates to create a vicious cycle that derails wound healing.

In recent years, another functional component of the neutrophil action response, the neutrophil extracellular traps (NETs), have been a focus of interest. Initially identified as being a beneficial neutrophilic response to pathogens such as bacteria, fungi and viruses,^{21–25} NETs are fibrous chromatin traps that sequester and kill a wide variety of microbes via release of granular components such as elastase, MPO, cathepsin G, lactoferrin and gelatinase.²⁶ Some critical triggers that have been implicated for this process, also called NETosis, include ROS²⁷ and an enzyme (peptidyl arginine deiminase 4 (PAD4)) that post-translationally modifies arginine residues on histones (H3 and H4) resulting in chromatin condensation.^{28–30} An interesting NETosis response to live *Staphylococcus aureus* infection was recently demonstrated *in vitro*, where nuclear material was rapidly released without cytoplasmic contents or lysis of plasma membrane.³¹ These denucleated neutrophils were shown to crawl and phagocytose the bacteria trapped in the created nuclear traps.^{32–34} The presence of anuclear neutrophils that are biologically active have been known since the 1980s³⁵ and possibly reflect a population of neutrophils that have undergone some aspect of NETosis. However, many questions remain to be answered in relation to specific mechanisms of activation of NETs in response to different stimuli such as biofilm infection.

As it relates to the overall inflammatory process elicited in response to injury, neutrophils are major players because they can modify macrophage function and therefore regulate innate immune response during wound healing.³⁶ In the absence of neutrophils, wound site macrophages seem to lack

guidance in conducting the healing process.³⁷ In a healing wound, neutrophil infiltration ceases after a few days of injury. Expended neutrophils are programmed to die and dying neutrophils are recognized by wound site macrophages and phagocytosed. The wound site contains a small portion of macrophages that are resident. Most macrophages at the wound site are recruited from the peripheral circulation. Extravasation of peripheral blood monocytes is enabled by the interaction between endothelial vascular cell adhesion molecule-1 and monocyte very late antigen-4 ($\alpha 4 \beta 1$ integrin). Factors that guide the extravasated monocyte to the wound site include growth factors, chemotactic proteins, proinflammatory cytokines, and chemokines such as macrophage inflammatory protein 1 α , MCP-1, and RANTES. The source of these chemoattractants includes clot-associated platelets, wound edge hyperproliferative keratinocytes, wound tissue fibroblasts and subsets of leukocytes already at the wound site. Once the monocyte leaves the blood vessel to transmute into the wound site through the ECM microenvironment, the process of monocyte differentiation to macrophages has started.

Mediators present in the microenvironment that the monocyte traverses to reach the wound site interact with receptors on the monocyte cell surface, bringing forth major changes in the transcriptomic as well as proteomic make up of the cell. Major examples of such receptors present on the monocyte surface include Toll-like receptors (TLRs; Fig. 13.7), complement receptors, and Fc receptors. At the wound site, macrophages function as antigen-presenting cells and phagocytes scavenging dead cells and debris. In addition, they deliver a wide range of growth factors that are known for their abilities to execute the wound-healing process. Such growth factors include TGF- β , TGF- α , basic FGF (bFGF), VEGF, and PDGF. These growth factors enable wound healing by causing cell proliferation and synthesis of ECM and inducing angiogenesis. Macrophages play a crucial role in enabling wound healing. Macrophage depletion is known to impair wound closure markedly.^{4,38}

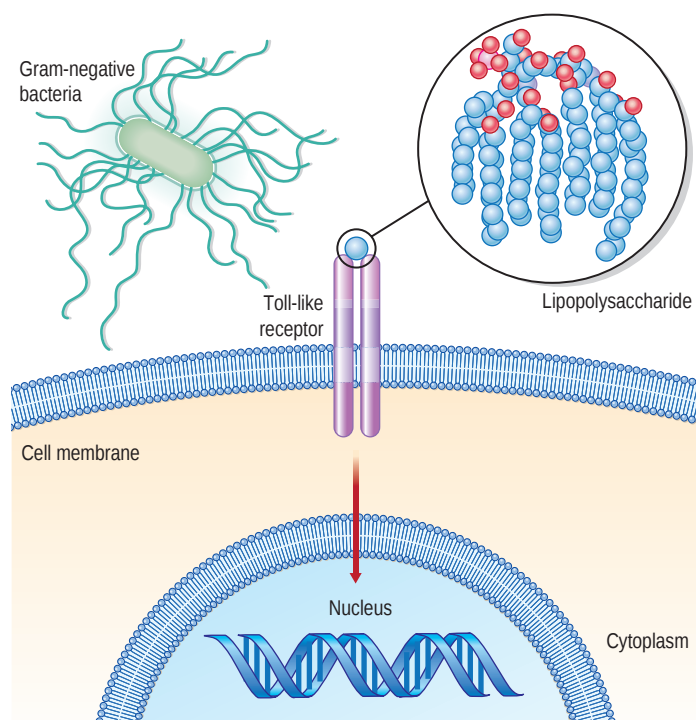


Fig. 13.7 Toll-like receptors: responding to infectious agents and the wound microenvironment.

Macrophages

Macrophages represent the predominant cell type in a healing wound 3–5 days following injury. The primary acute function of wound macrophages, which arrive at an injury site hours later than neutrophils, is to operate as voracious phagocytes cleansing the wound of all matrix and cell debris, including fibrin and apoptotic neutrophils. Macrophages also produce a range of cytokines, growth and angiogenic factors that drive fibroblast proliferation and angiogenesis.^{4,39–42} In a classic study, Leibovich and Ross⁴³ demonstrated that antimacrophage serum combined with hydrocortisone diminished the accumulation of macrophages in healing skin wounds of adult guinea pigs. Such depletion resulted in impaired disposal of damaged tissue and provisional matrix, compromised fibroblast count, and delayed healing. Today, macrophages have emerged to be a pivotal driver of efficient skin repair.^{44,45} Monocyte-derived macrophages are highly plastic and can differentiate into proinflammatory (M1) or anti-inflammatory/pro-reparative (M2) phenotypes that can also transdifferentiate into other cell types based on environmental cues and molecular mediators.^{46,47} The macrophage population first taking part in inflammation may change its phenotype to a more anti-inflammatory macrophage and assume the role to resolve inflammation.^{48,49} Macrophages from diabetic wounds display dysfunctional inflammatory responses.⁵⁰ A persistent inflammatory state of diabetic wound macrophages is caused by impairment in the ability of these cells to phagocytose apoptotic cells at the wound site which in turn prevents the switch from M1 to M2 phenotype.⁵⁰ Recently, given the lack of standard, all-encompassing descriptors for macrophages, a collaborative effort was initiated to re-define macrophage nomenclature to encompass the scope of diversity known to

exist in macrophage activation. The proposed nomenclature change would involve inclusion of activation standards based on the source of the activator, be it cytokines such as IL-4, IL-10 or bacterial lipopolysaccharide (LPS) (e.g. M(IL-4), M(IL-10), M(LPS), etc., where M refers to macrophage) and where relevant, a combination of macrophage-specific surface markers or lack thereof to describe activation outcomes.⁵¹

Mast cells

Mast cells are best known for their central role in mediating allergic responses. Beyond that function, it is now known that mast cells are physiologically significant in recognizing pathogens and in regulating immune response.⁵² Mast cells may instantly release several proinflammatory mediators from intracellular stores. In addition, they are localized in the host–environment interface. These properties make mast cells key players in fine-tuning immune responses during infection. Recent studies using mast cell activators as effective vaccine adjuvants show the potential of harnessing these cells to confer protective immunity against microbial pathogens.⁵³ Mast cell activation helps initiate the inflammatory phase of wound healing. In response to injury, mast cells at the wound site degranulate within a matter of hours and therefore become histologically silent at the wound tissue. After about 48 hours of injury, mast cells are again seen in the wound tissue and their number increases as healing progresses.⁵⁴ On one hand, impaired wound healing has been reported in mast cell-deficient mice.⁵⁵ On the other hand, mast cells have been implicated in skin wound fibrosis.⁵⁶ With the aid of a wide array of newly formed or preformed mediators released by degranulation, the activated mast cell controls the key events of the healing phases: triggering and modulation of the inflammatory stage, proliferation of connective cellular elements, and final remodeling of the newly formed connective tissue matrix. The importance of the mast cell in regulating healing processes is also demonstrated by the fact that a surplus or deficit of degranulated biological mediators causes impaired repair, with the formation of exuberant granulation tissue (e.g., keloids and hypertrophic scars), delayed closure (dehiscence), and chronicity of the inflammatory stage.⁵⁷

Resolution of inflammation

Inflammatory responses elicited by injury are only helpful to the healing process if they are timely and transient. Dysregulated inflammation complicates wound healing and prevents progression of the wound healing cascade beyond the inflammatory phase.⁵⁸ For resolution of inflammation to ensue, further leukocyte recruitment must be halted and accompanied by removal of leukocytes from inflammatory sites. At the wound site successful phagocytosis of dead neutrophils by macrophages is a key factor. Impairment in macrophage function, as is commonly seen with diabetes, derails the resolution of inflammation.⁵⁸ Lipid mediators, such as the lipoxins, resolvins, protectins, and newly identified maresins, have emerged as a novel genus of potent and stereoselective players that counterregulate excessive acute inflammation and stimulate molecular and cellular events that define resolution.⁵⁹ Successful resolution paves the path for the healing process to progress towards successful wound closure. Prolonged inflammation may not only compromise wound closure but may also worsen scar outcomes.⁶⁰ The inappropriate and

sustained levels of inflammation observed in various chronic wound states could be induced by microbial biofilms and certainly contribute to derailing the wound healing process.⁶¹ Bacteria come armed with various virulence factors that stimulate a proinflammatory response in the wound microenvironment that interfere with the normal pattern of host responses. Details on the role of infection, particularly bacterial biofilm infection in wound healing, are covered in the section on [chronic wounds](#).

Proliferative phase

The proliferative phase starts around 2 days after injury and normally lasts up to 3 weeks in a healing cutaneous wound. This phase overlaps with the inflammatory phase and supports re-epithelialization, the formation of new blood vessels, and the influx of fibroblasts and laying down of the ECM. By the time this phase begins, the degradation of the fibrin clot by the macrophages has begun and invading endothelial cells and fibroblasts rapidly fill that space. Migrating fibroblasts produce the cytokines that induce keratinocytes to migrate and proliferate.⁶² Activated macrophages produce several cytokines, such as PDGF and TNF- α , which also induce fibroblasts to produce keratinocyte growth factor which in turn induces wound re-epithelialization.^{63,64}

Granulation tissue

The fibrin clot formed during hemostasis participates in the early inflammatory phase and is replaced by a perfused, fibrous connective tissue that grows from the base of a wound and is able to fill wounds of almost any size. During the proliferative phase of wound healing, this granulation tissue is light red or dark pink in color because of perfusion by new capillary loops. It is soft to the touch, moist, and granular in appearance. The granulation tissue serves as a bed for tissue repair. The ECM of granulation tissue is created and modified by fibroblasts. Initially, it consists of a network of type III collagen, a weaker form of the structural protein that can be produced rapidly. This is later replaced by the stronger, long-stranded type I collagen, as evidenced in scar tissue. Formation and contraction of the granulation tissue represent integral aspects of the healing wound. In ischemic wounds, production and contraction of the granulation tissue is impaired because of decreased ATP production, impaired collagen synthesis and failure to convert the fibroblast phenotype into a myofibroblast to promote wound contraction.⁶⁵

Vascularization

Wounds complicated by underlying ischemia largely rely on wound vascularization for their closure. Wound vascularization may be achieved by angiogenesis or vasculogenesis. Angiogenesis represents sprouting of capillaries from existing blood vessels in the wound edge tissue. Vasculogenesis relies on the formation of new blood vessels by mobilization of bone marrow-derived endothelial stem cells.

Wound vascularization is regulated by all phases in wound healing – hemostasis, inflammation, tissue formation, as well as tissue remodeling. The hemostatic plug provides a bed to attract blood-borne cells to the wound site. Once cells entangle in this plug, the ECM environment modifies cell function

towards successful healing. Platelets in the clot serve as a source of growth factors and cytokines, which recruit several cell types, including endothelial cells, to the wound site. During the inflammatory phase, leukocytes at the wound site serve as a major source of pro-angiogenic factors such as VEGF-A and IL-8 that lay the early foundation for successful wound tissue vascularization. As neutrophils are expended and undergo cell death, the number of macrophages at the wound site substantially increases. Macrophage-derived TGF- β , TGF- α , bFGF, PDGF, and VEGF play a key role in driving skin wound angiogenesis. Growing evidence demonstrates that no single angiogenic factor is singularly effective in significantly influencing wound outcomes. Wound vascularization is a sophisticated process requiring dynamic, temporally and spatially regulated interaction between cells, angiogenic factors, and the ECM.

Key processes in tissue vascularization are depicted in [Fig. 13.8](#). Angiogenic cues are elicited by microenvironmental signals such as hypoxia and are amplified by angiogenic factors such as VEGF expressed by and released from cells at the wound site. VEGF was originally identified as an endothelial cell-specific growth factor stimulating angiogenesis and vascular permeability. Some family members, VEGF C and D, are specifically involved in lymphangiogenesis. Ligation of these angiogenic factors with their corresponding receptors elicits a multitude of cell-signaling processes that activate microvascular endothelial cells. For example, VEGFs and their endothelial tyrosine kinase receptors are central regulators of tissue vascularization. VEGF signaling through VEGFR-2 is the major angiogenic pathway. VEGFR-3 has also been shown to be important for angiogenesis, acting together with VEGF/VEGFR-2 and Dll4/Notch signaling to control angiogenic sprouting.⁶⁶ The biological significance of other angiogenic factors such as EGF and bFGF is mediated by their corresponding receptors, which also belong to the family of tyrosine kinase receptors EGFR, FGFR-1, FGFR-2, FGFR-3, and FGFR-4.

Other tyrosine kinase receptors of outstanding significance in this regard are Tie-1 and Tie-2. Along with the VEGF receptor, these are the only known endothelial cell-specific receptor tyrosine kinases. Tie-2 is induced on the endothelium of neovessels in skin wounds and downregulated as newly formed vessels regress. As an indicator of Tie-2 activation, Tie-2 phosphorylation is detected in skin wounds at all stages of the healing process.⁶⁷ Activated microvascular endothelial cells respond by proliferating, which is followed by directional migration of these cells. Migration is a complex process in which cells move in a given direction either in response to changes in the extracellular environment or as a consequence of an intrinsic propensity for directional movement. ECM remodeling by proteases promotes cell migration, a critical event in the formation of new vessels. Temporal and spatial regulation of ECM remodeling events allows for local changes in net matrix deposition or degradation, which in turn contributes to control of cell growth, migration, and differentiation during different stages of angiogenesis. Matrix-bound growth factors released by proteases and/or by angiogenic factors promote angiogenesis by enhancing endothelial migration and growth. Matrix molecules promote endothelial cell growth and morphogenesis, and/or stabilize nascent blood vessels. Hence, ECM molecules and ECM remodeling events play key roles in regulating angiogenesis.⁶⁸

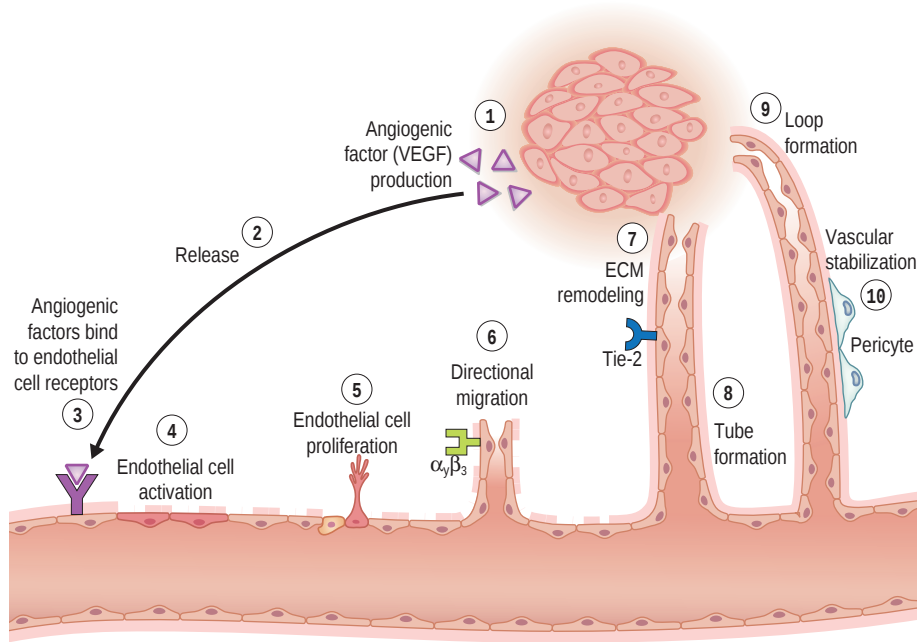


Fig. 13.8 Neoangiogenesis: the formation of new blood vessels. VEGF, vascular endothelial growth factor; ECM, extracellular matrix.

The formation of the capillary-like tubes is specific to endothelial cells and integral to the process of angiogenesis. The basement membrane represents a biologically functional highly specialized ECM on which the basal non-luminal surface of endothelial cells rests. This matrix forms a continuous sleeve around the endothelial cells, and maintains the tube-like structures of the blood vessels. More than 20 years ago Kubota *et al.* observed that endothelial cells plated on a reconstituted basement membrane matrix, rapidly attached, aligned, and formed capillary-like tubules. The cells did not proliferate. The vessels that are thus formed contain a lumen and tight cell-cell contacts. The cells are polarized with the nuclei basally located towards the basement membrane matrix. Furthermore, the capillary-like structures take up acetylated low-density lipoprotein, which is a marker of differentiation for these cells.⁶⁹ Angiogenesis not only depends on endothelial cell invasion and proliferation, but also requires pericyte coverage of vascular sprouts for vessel stabilization. These processes are coordinated by VEGF and PDGF through their cognate receptors on endothelial cells and vascular smooth-muscle cells, respectively.⁷⁰ Structural support to blood vessels is provided to pericytes and vascular smooth-muscle cells. Normal pericytes are embedded within the basement membrane of capillaries, either as solitary cells or a single-cell layer, where they coordinate intercellular signaling with endothelial cells and other components of the blood vessel wall to prevent leakage. In contrast, vascular smooth-muscle cells form single or multiple layers around arteries and veins to mediate vascular tone and contraction. Pericyte coverage is required for the stabilization of immature endothelial tubes.⁷¹ Pericytes have functions beyond angiogenesis that are relevant to wound healing. Skin pericytes are very plastic and may act as mesenchymal stem cells (MSCs), exhibiting the capacity to differentiate into bone, fat, and cartilage lineages. Thus, pericytes represent a potent stem cell population in the skin that is capable of modifying the ECM

microenvironment and promoting epidermal tissue renewal from non-stem cells.⁷²

Wound closure

Wound contraction and re-epithelialization contribute to closure of wounds that heal by secondary intention. Wound contraction represents an early response to injury that is aimed at juxtaposing the edges of an open wound.⁷³ This early phase of wound closure appears to be mediated by a contractile “purse-string” force produced by a circumferentially arranged band of fusiform-shaped epidermal cells situated in the wound margin.⁷⁴ Fibroblasts at the wound edge tissue are recognized to play a key role in enabling wound contraction.⁷⁵ During the inflammatory phase of wound healing, fibroblasts acquire smooth-muscle cell characteristics and differentiate into contractile myofibroblasts. The first phenotypic transition of wound edge fibroblasts into so-called protomyofibroblasts is characterized by neoformation of contractile β -cytoplasmic actin stress fibers and occurs in response to profibrotic cytokines and to altered properties of the ECM. In the presence of TGF- β 1 in a mechanically restrained environment, these cells express α -smooth-muscle actin *de novo*, which significantly increases their contractile activity and is a hallmark of the differentiated myofibroblast.⁷⁶ Wound contraction may significantly contribute to wound closure, although this contribution is much larger in loose-skinned rodents than in humans.

In an open wound that has undergone contraction, restoration of an intact epidermal barrier is enabled through wound epithelialization, also known as re-epithelialization.^{77,78} A wound that is not epithelialized is not considered “healed”, no matter how perfectly restored the underlying dermal structures may be. Thus, wound epithelialization is a critical and defining feature of wound repair. Re-epithelialization of

the wound can be conceptually viewed as the result of three overlapping keratinocyte functions: migration, proliferation, and differentiation. The sequence of events by which keratinocytes accomplish the task of re-epithelialization is generally believed to begin with dissolution of cell–cell and cell–substratum contacts. This is followed by the polarization and initiation of directional migration in basal and a subset of suprabasilar keratinocytes over the provisional wound matrix. A subset of keratinocytes immediately adjacent to, but not within, the wound bed then undergoes mitosis. Finally, there is multi-layering of the newly formed epidermis and induction of differentiation-specific gene products to restore the functionality of the epidermis. The most limiting factor in wound re-epithelialization is migration, since defects in this function, but not in proliferation or differentiation, are associated with the clinical phenotype of chronic non-healing wounds.⁷⁹ The process of epithelialization continues until the barrier is re-established and the wound is covered. The process of re-epithelialization is accelerated by a moist environment^{80,81} and is facilitated by the enzyme matrix metalloproteinase 1, a collagenase which lessens the affinity of the collagen–integrin contacts.⁸²

MicroRNAs

Wound healing is largely dependent on injury-inducible protein-coding genes as they serve as drivers of an inherent tissue repair program that seeks to restore the injured tissue both structurally as well as functionally. There are two key steps that separate a protein-coding gene from its corresponding protein. First, the DNA hosting the gene must transcribe to mRNA and second, the mRNA must be translated to protein. Work emerging during recent years demonstrates that both of these critical steps are subject to robust and redundant regulation by microRNAs (miRNAs: 19–22 nucleotides long), which are noncoding RNAs found in all eukaryotic cells. Work during the past decade recognizes small RNAs as a new class of regulators of eukaryotic biology that could be classified as epigenetic regulators of gene expression.⁸³ Alongside other small interfering RNAs (siRNAs), miRNAs execute post-transcriptional gene silencing through mRNA destabilization as well as translational repression. In simple terms, whether a gene would code a protein or not is decided by miRNAs for which the gene is a target. miRNAs form base pairs with specific sequences in protein-coding mRNAs. Near-perfect pairing induces cleavage of the target mRNA, whereas partial pairing results in translational repression and mRNA decay through deadenylation pathways.⁸⁴ According to the miRbase database, the human genome encodes 1881 miRNAs. This count is rapidly growing. These miRNAs may regulate more than a third of all protein-coding genes and virtually all biological processes. Mammalian cells express cell type-specific miRNAs which silence unique subsets of target genes within the cell. While miRNAs are mostly known for being functional in the cytoplasm, nuclear miRNAs may also participate in gene regulation. Initially considered an oddity, miRNA-dependent control of gene expression is now accepted as being integral to the normal function of cells and organisms.⁸⁵ miRNAs are emerging as key regulators of the overall wound-healing process.^{86–88} miRNA dependent regulation of processes as it relates to wound healing are discussed

in subsequent sections in this chapter. The regulation of a variety of functionally related genes by modulating a single miRNA holds promise for miRNA-based therapeutics. As the knowledge of specific roles of miRNAs continues to grow, the emergence of miR-based therapies that specifically upregulate beneficial miRs and/or downregulate potentially harmful miRs will emerge as useful tools in the clinic. miRNA dependent regulation of specific phases in wound healing are mentioned in the section on [chronic wounds](#).

Acute wounds

Any violation of live tissue integrity may be regarded as a wound. Skin is the largest organ of the human body, covering about 3000 square inches (7620 cm²) in an average adult. The most important role of the skin for terrestrial animals is to protect the water-rich internal organs from the dry external environment. As a primary line of defense against external threats, maintenance of integrity of the skin is a key prerequisite for healthy survival. Thus, healthy skin can regenerate and repair itself under most common conditions. Skin wounds may be open when manifested as a tear, cut, or puncture. Blunt force trauma may cause closed wounds or contusion where the skin appears to be intact but suffers from damage caused to underlying tissues.

Open wounds may be generally categorized as:

- Lacerations – ragged tears and cuts; masses of torn tissue underneath; caused by dull knife, bomb fragments and machinery and may include crushing of tissues; frequently contaminated ([Fig. 13.9](#))
- Puncture – e.g., sharp penetrations caused by nails, needles, wire, or bullets (see [Fig. 13.9](#)). These are of great concern in patients with diabetes, as many of these patients have polyneuropathy and have insensate feet, leading to occult injury. Many times these patients will step on thumb tacks, safety pins, or other sharp household objects and not even know it: this, coupled with compromised vascular status, leads to chronic wound infection
- Abrasions – the superficial layer of the skin is removed; skinned knee or elbows and rope burns are examples; an abrasion lends itself to infection

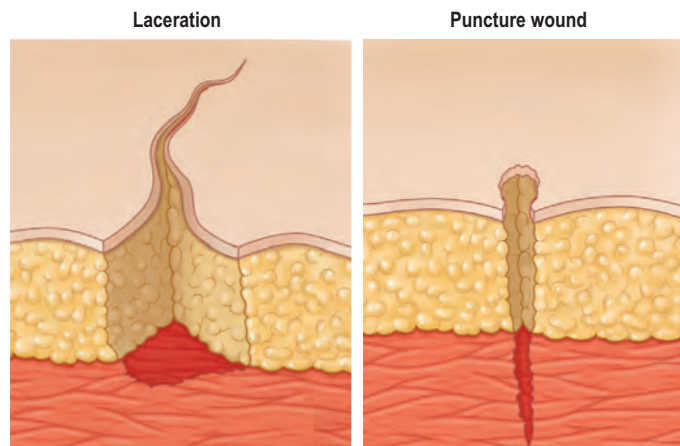


Fig. 13.9 Laceration and puncture wounds.

- Avulsions – sections of skin torn off either in part (attached to body) or totally (detached from body); heavy bleeding is common
- Amputations – traumatic amputation results in nonsurgical removal of limb from the body and accompanies heavy bleeding.

There are three general techniques of wound treatment:

1. Primary intention, in which all tissues, including the skin, are closed with suture material after completion of the operation
2. Secondary intention, in which the wound is left open and closes naturally
3. Tertiary intention, in which the wound is left open for a number of days and then closed if it is found to be clean.

Factors that promote healing

Nutrition

The importance of adequate nutrition to supplement and sustain the energy-intensive process of wound healing has been established for many years.^{89–92} The need for nutrients such as carbohydrates, protein, fat, amino acids, vitamins and mineral supplements is underscored by the observations that in malnutrition conditions or lack of sufficient nutritional supplementation, processes critical to wound healing are impeded. These include delayed neovascularization, decreased collagen synthesis leading to impaired mechanical strength of the skin and prolonged inflammation leading to dysfunctional immune responses.^{89,93–96} Since the identification of malnutrition as a reversible risk factor for pressure ulcer development,⁹⁷ recommendations have been made for the inclusion of validated nutrition screening and assessment tools to determine nutritional status. Serum pre-albumin (transerythrin) has a shorter half-life than albumin and may serve as a more sensitive indicator of changes in protein-energy status. It is recommended as a good screening tool for malnutrition if used as two measurements taken 3–5 days apart along with CRP levels.⁹⁸

Fats (particularly short chain fatty acids (SCFAs) such as butyrates, acetate and propionate) and carbohydrates (such as glucose) provide the primary energy source for collagen synthesis and deposition and angiogenesis. The American Society for Parenteral and Enteral Nutrition and the Wound Healing Society guidelines for optimal wound healing recommends 30–35 kcal.kg⁻¹.d⁻¹ for normal, healthy adults and 35–40 kcal.kg⁻¹.d⁻¹ for adults suffering from malnutrition.

Fibroblast proliferation, collagen deposition, formation of vascular supply and immune responses are dependent on the availability of proteins, which are the building blocks of wound repair. The recommended range of protein intake for wound healing is 0.8–1 g.kg⁻¹.d⁻¹ in normal adults and higher (up to 2 g.kg⁻¹.d⁻¹) for chronic wound patients. The amino acids arginine and glutamine have been studied for their roles in wound healing, particularly related to collagen deposition, angiogenesis and immune function.^{89,93,99–101} However, it still remains unclear how essential these and other amino acids are in specific aspects of wound healing.

Vitamins A, C and E have potent antioxidant and anti-inflammatory effects that are implicated in promoting proper tissue repair. The stimulation of immune responses,

re-epithelialization, and collagen deposition have all been linked to the presence of adequate levels of each of these vitamins independently.⁹⁵

Micronutrients such as magnesium, copper, zinc and iron serve as co-factors particularly for enzymes that support the wound healing process.^{89,93,99}

Therapeutic oxygen

Oxygen directly impacts wound healing by targeting numerous molecular targets and cell types. Increased fibroblast proliferation and migration, increased collagen synthesis and the resulting increase in the tensile strength of collagen fibers, stimulation of angiogenesis, promotion of immune functions such as macrophage chemotaxis, leukocyte antibacterial and physiological wound debridement functions are all attributed to the essential role of oxygen in healing wounds.^{102,103} Therefore, the use of direct oxygen supplementation to improve wound healing is a natural extension of these observations. The therapeutic oxygen modalities that are used to treat wounds are described in more detail in later sections in this chapter.

Chronic wounds

Factors that drive wound chronicity

Infection and biofilm

Infection is a common problem in chronic wounds, frequently resulting in non-healing and significant patient morbidity and mortality.¹⁰⁴ Wound infection and the subsequent release of proinflammatory modulators result in pain and delayed healing. The pain, in turn, compromises the immune response to infection.¹⁰⁵ All wounds become contaminated by bacteria from the surrounding skin, the local environment, and autologous patient sources. The local environment is particularly relevant for hospitalized patients. Colonization is defined as the presence of proliferating bacteria without a noticeable host response. Colonization of the wound may enhance or impede wound healing, depending upon the bacterial load. Bacterial loads in excess of 10⁵ organisms per gram of tissue are a threat to wound healing, although this threshold may be altered by the status of the host immune system and the number and types of bacterial species present. The concept of critical colonization, characterized by increased bacterial burden or covert infection, is controversial and not universally accepted. Substantial colonization may not cause obvious signs of inflammation, but may affect wound healing with failure to heal or slowing of progression. Signs of critical colonization are atrophy or deterioration of granulation tissue, discoloration of granulation tissue to deep red or gray, increased wound friability, and increased drainage. The transition to infection occurs when bacterial proliferation overcomes the host's immune response and host injury occurs. Several factors determine transition from colonization to infection: the bioburden itself, the virulence of the organisms, the synergistic action of different bacterial species, and the ability of the host to mount an immune response.¹⁰⁴

During the past decade, there has been rapid progress in the understanding of innate immune recognition of microbial

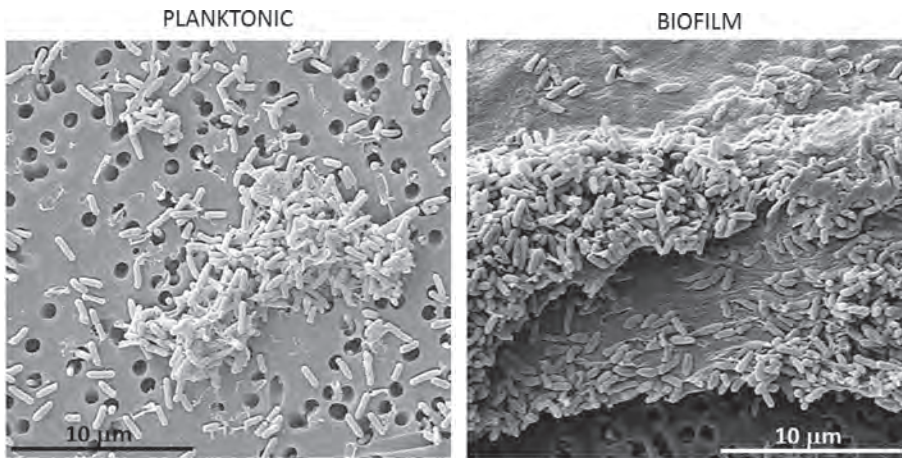


Fig. 13.10 Scanning electron microscopy (SEM) images of planktonic and biofilm mode of the Gram-negative pathogen *Pseudomonas aeruginosa*.

components and its critical role in host defense against infection. The early concept of innate immunity was that it non-specifically recognized microbes; however, the discovery of TLRs (Fig. 13.7) in the mid-1990s showed that pathogen recognition by the innate immune system is instead actually specific, relying on germline-encoded pattern recognition receptors (PRRs) that have evolved to detect components of foreign pathogens, referred to as pathogen-associated molecular patterns (PAMPs).¹⁰⁶ TLRs regulate innate and adaptive immune responses and are important modulators of inflammation during wound-healing responses. The finding that there is activation of TLR signaling during tissue damage in several disease situations in the absence of infection suggests that endogenous molecules serve as TLR agonists, although it is unclear whether this response is biologically important for maintenance of homeostasis, such as tissue repair, or whether this recognition is simply accidental. It is noteworthy that microbial infection triggers the production of modified endogenous molecules (such as high-mobility group protein B1, oxidized phospholipids, β -defensin 2, and nucleic acids) that are recognized by TLRs or other cytosolic PRRs. This may suggest that these endogenous molecules, along with PAMPs, act as adjuvants to activate innate immune programs via TLRs and/or other PRRs, and have key roles in facilitating adaptive immunity against infecting microbes.

Chronic wounds have a complex colonizing flora that changes over time. *Staphylococcus aureus* and coagulase-negative staphylococci are the most commonly isolated organisms. Chronic wounds are colonized by multiple bacterial species and many persist in the wound once they are established. In chronic venous leg ulcers the most common bacteria noted, in order of abundance, were *S. aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, coagulase-negative staphylococci, *Proteus* spp., and anaerobic bacteria. Resident (colonizing) bacterial species are commonly present in ulcers. The longer an ulcer remains unhealed, the more likely it will acquire multiple aerobic organisms and a significant anaerobic population. Chronic wounds are commonly complicated by localized ischemia because of disruption of the vessels at the site of tissue injury. Thus, they tend to have a low tissue oxygen level. This facilitates the growth of anaerobes in ischemic wounds. Adequate delivery of oxygen to the wound tissue is vital for optimal healing and resistance to infection.¹⁰⁷ Hospitalization, surgical procedures, and prolonged or

broad-spectrum antibiotic therapy may predispose patients to colonization or infection, or both, with resistant organisms, including *S. aureus* (methicillin-resistant *S. aureus* – MRSA) or vancomycin-resistant enterococci (VRE).¹⁰⁸ Inflammatory responses to microbial invasion may be diminished in persons with diabetes or other immunosuppressive conditions.¹⁰⁸

Microorganisms do not always live as pure cultures of dispersed single/planktonic cells but instead accumulate at interfaces to form polymicrobial aggregates such as films, mats, flocs, sludge, or biofilms (Fig. 13.10). The biofilm state of microorganisms may lead to an increase in virulence and resistance to antibiotic therapy and evasion of host immune response. In most biofilms, the microorganisms account for less than 10% of the dry mass, whereas the matrix can account for over 90%. The matrix is the extracellular material, mostly produced by the organisms themselves, in which the biofilm cells are embedded. It consists of a conglomeration of different types of biopolymers – known as extracellular polymeric substances (EPS) – that aid in adhesion to surfaces, form the scaffold for the developing biofilm and also provide a physical barrier that is relatively impenetrable to antimicrobial substances and immune responses. The formation of a biofilm allows a lifestyle that is entirely different from the planktonic state. Although the precise and molecular interactions of the various secreted biofilm matrix polymers have not been defined, several functions of EPS have been determined, demonstrating a wide range of advantages for bacteria in a biofilm state. The architecture of biofilms as determined by *in vitro* studies is influenced by many factors, including hydrodynamic conditions, concentration of nutrients, bacterial motility, and intercellular communication, as well as exopolysaccharides and proteins.¹⁰⁹ These studies involving the use of abiotic (e.g. Calgary biofilm device, modified Robbins device, Bioflux systems, etc.) or biotic surfaces (e.g. reconstituted human epithelia (RHE), Lubbock model, tissue-engineered equivalents such as Graftskin) have helped to understand numerous mechanistic aspects of biofilm growth such as intercellular communication involving quorum sensing, antimicrobial tolerance and also testing the efficacy of antibiofilm therapeutics. However, the clinical relevance of these studies is limited because of the inability to address the iterative host response to the presence of biofilm that defines the establishment of chronic infection. *In vivo* studies on biofilms have included a range of model organisms from the common

fruit fly (*Drosophila melanogaster*) to vertebrates such as rats, mice, rabbits and pigs, each with its own advantages and disadvantages.^{110,111} The high homology between porcine and human skin, the similarities in the immune responses compared to rodent models and the observation that in relation to wound therapies, porcine studies were in agreement with humans 78% of the time compared to 53% and 57% with rodents and *in vitro*, respectively, make the porcine model translationally relevant as recommended by the Wound Healing Society.¹¹² Recently, a chronic wound biofilm model was developed with the goal of understanding long term host-biofilm interactions that drive wound chronicity. This model was used to demonstrate that persistent biofilm infection compromised wound healing by interfering with tight junction proteins that are critical for maintenance of skin barrier function.¹¹³

Wounds provide an ideal environment for biofilm development. The extracellular matrix components such as collagen, fibronectin and laminin could serve as ligands for attachment of bacteria to initiate colonization. Wound beds are moist and nutritious and provide the conditions that would allow micro colonies of bacteria to develop surrounded by the protective barrier of the matrix provided the initial colonization is successful. In fact, it is estimated that 60% of chronic human wounds are infected with biofilm bacteria emphasizing an important role for the sessile, aggregated mode of bacterial growth as factors in chronicity.¹¹⁴ Compared to bacteria in the unattached free-living planktonic form, bacteria that reside within mature biofilms are highly resistant to traditional antibiotic therapies. Bacteria in biofilms grow more slowly, and slower growth may lead to decreased uptake of the drug and other physiologic changes that could impair drug effectiveness.¹⁰⁹

There are several features of biofilm infection in wounds that represent significant clinical and diagnostic challenges. First, bacteria in a biofilm state cannot be cultured reliably using standard culture methods and the gram stain frequently will not show inflammatory cells, so even when bacteria are seen on the gram stain they are diagnosed as colonizing organisms not pathogens. In a case series of sternal wound infections only two out of six patients with staphylococcal biofilm infection had positive cultures, but staphylococcal biofilm was detected on sternal wires in all six patients using scanning electron microscopy.¹¹⁵ Second, debridement alone does not effectively eradicate biofilm infection. It can drive biofilm-producing bacteria deeper into the surrounding tissue with recurrence of biofilm infection within 7 days.¹¹³ Additionally, aberrant host immune responses to biofilm infection are implicated in the persistence of infection and wound chronicity.^{61,116–124} Biofilms of *Pseudomonas* and *Staphylococcus* spp. trigger the host response by recruitment of polymorphonuclear leukocytes to the sites of the biofilm. However, after recruitment, these host cells are frustrated in their expected function of clearing the infection because of biofilm-specific arsenal such as alginate and rhamnolipids (*Pseudomonas* specific) or polysaccharide intercellular adhesins (PIA, *Staphylococcus* specific) that hold the host response at bay.¹²³ By definition bacteria in a biofilm state are adherent to a surface, e.g. a catheter, an implant, soft tissue or bone in a wound¹²⁴, so they will not result in bacteremia and systemic illness. Since scanning electron microscopy is not clinically available, and current culture methods are unreliable, the diagnosis of

biofilm infection is based primarily upon clinical findings. Biofilm infection is the clinical paradigm that can be consistently applied to all chronic wounds and likely represents a unifying pathologic feature. Therefore, there is a strong need to understand the clinical biofilm.

Determining clinical endpoints

The FDA defines **complete wound closure** of chronic non-healing wounds as “skin closure (as assessed visually) without drainage or dressing requirements identified at two consecutive study visits that are 2 weeks apart” and requires therapeutic trials for chronic wounds to be designed such that the enrolled patients will be evaluated for at least 3 months following complete closure.¹²⁵ Here, the expectation is that successful intervention should keep the wound closed for at least 90 days. The determination of wound closure is based primarily on visual assessments. However, such visually closed wounds are sometimes prone to post-closure complications such as recurrence. Indeed high recurrence rates have been reported for chronic wounds (40–79% for pressure ulcers (PUs), 24–57% for venous leg ulcers (VLUs) and upward of 60% for diabetic foot ulcers (DFUs)).^{126–131} Recent evidence indicates that biofilm-infected wounds appear visually closed, but remain functionally open (high transepidermal water loss (TEWL_{hi})) because of elevated levels of biofilm-induced microRNAs (miR-146a and miR-106b) and dysregulated tight junction proteins (ZO-1 and ZO-2) (Fig. 13.11). This challenges the current assessment of visual wound closure and emphasizes the need for additional measurements such as TEWL in the objective and comprehensive monitoring of wound healing.¹¹³

miR regulation of skin barrier function

Evidence from Dicer ablation and microRNA overexpression studies in the intestinal epithelium have supported roles for miRNA regulation of epithelial barrier function.¹³² In the cutaneous epithelium, recent studies have identified roles for miRs in the regulation of skin barrier function. miR-dependent silencing of cellular tight junction proteins resulting in compromised epithelial barriers was recently identified and miR-146a was validated to directly target ZO-1 and ZO-2,¹¹³ key tight junction proteins that are essential for the establishment of proper junctional connections between skin cells^{133–135} that contribute to proper skin barrier function. miR-146a along with miR-106b were also identified as being biofilm inducible. More recently, keratinocyte-specific Dicer ablation studies in a mouse model also supported roles for the miRNA regulatory pathway in proper establishment of barrier function via the p21^{waf1/Cip1} pathway following wounding.¹³⁶

Ischemia and tissue oxygenation

Vascular complications commonly associated with problematic wounds are primarily responsible for wound ischemia. Limitations in the ability of the vasculature to deliver O₂-rich blood to the wound tissue lead to, among other consequences, hypoxia. Hypoxia is a reduction in oxygen delivery below tissue demand, whereas ischemia is a lack of perfusion, characterized not only by hypoxia but also by insufficient nutrient supply.¹⁰³ Hypoxia, by definition, is a relative term. It is

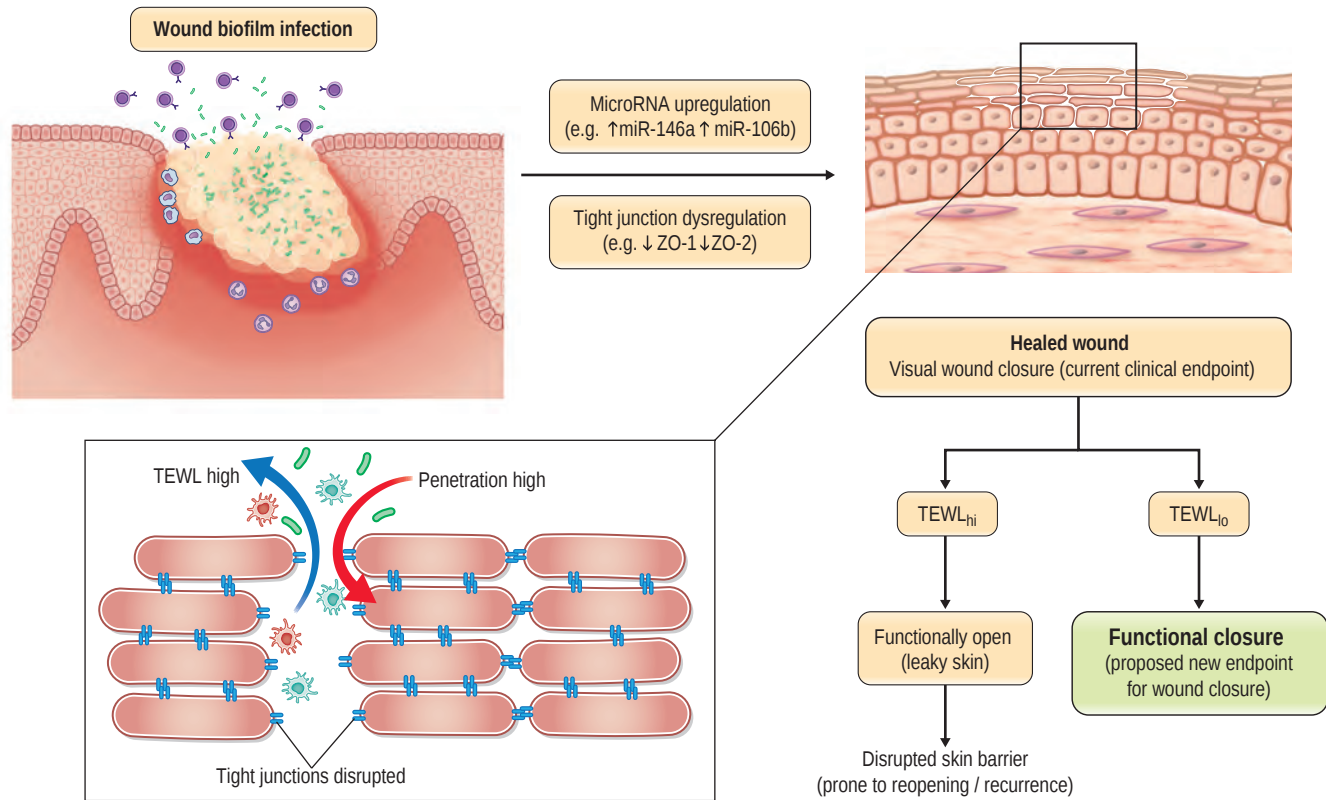


Fig. 13.11 Induction of biofilm-inducible miRs in infected wounds followed by silencing of tight junction proteins ZO-1 and ZO-2, results in compromised skin barrier function indicated by high transepidermal water loss (TEWL) measurements (TEWL_{hi}). Such wounds may appear to be visually closed but are functionally open (leaky/failed skin).

defined by a lower tissue partial pressure of oxygen (pO_2) compared to the pO_2 to which the specific tissue element in question is adjusted under healthy conditions *in vivo*. Depending on the magnitude, cells confronting hypoxic challenge either induce an adaptive response that includes increasing the rates of glycolysis, conservation of energy or progression to cell death. Generally, acute, mild to moderate hypoxia supports adaptation and survival. In contrast, chronic, extreme hypoxia leads to tissue loss.

While tumor tissue is metabolically designed to thrive under conditions of hypoxia, hypoxia of the wound primarily caused by vascular limitations is intensified by coincident conditions (e.g., infection, pain, anxiety and hyperthermia) and leads to poor healing outcomes. Oxygen and its reactive derivatives (Fig. 13.12) are required for oxidative metabolism-derived energy synthesis, protein synthesis, and the maturation (hydroxylation) of extracellular matrices such as collagen. Molecular oxygen is also required for nitric oxide (NO) synthesis which in turn plays a key role in the regulation of vascular tone as well as in angiogenesis. In a wound setting, large amounts of molecular oxygen are partially reduced to form reactive oxygen species (ROS). ROS include oxygen free radicals such as superoxide anion as well as its non-radical derivative, hydrogen peroxide (H_2O_2). Superoxide anion radical is the one-electron reduction product of oxygen. NADPH oxidases represent one major source of superoxide anion radicals at the wound site. NADPH oxidases in phagocytic cells help fight infection. Superoxide anion also drives endothelial cell signaling such as that required during

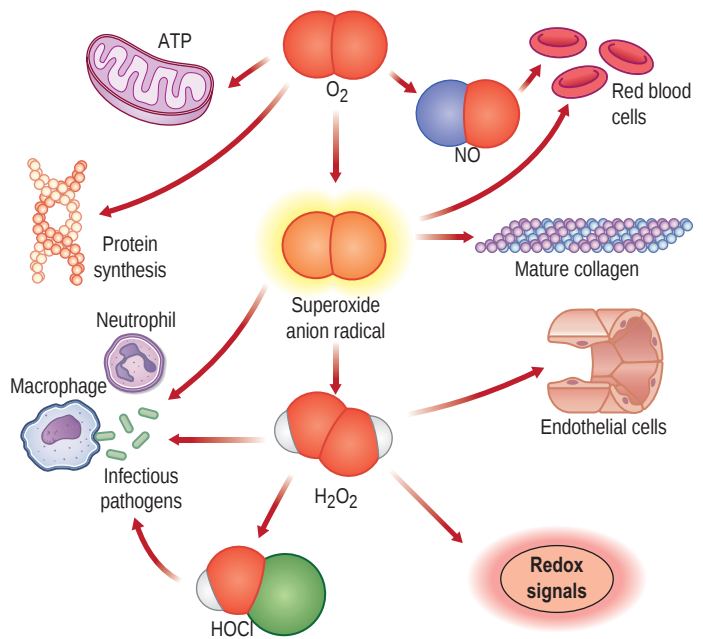


Fig. 13.12 Molecular oxygen and its derivatives in wound healing. ATP, adenosine triphosphate; NO, nitric oxide.

angiogenesis. In biological tissues, superoxide anion radical rapidly dismutates to hydrogen peroxide, either spontaneously or facilitated by enzymes called superoxide dismutases. Endogenous hydrogen peroxide drives redox signaling, a molecular network of signal propagation that supports key aspects of wound healing such as cell migration, proliferation, and angiogenesis. Neutrophil-derived hydrogen peroxide may be utilized by MPO to mediate peroxidation of chloride ions, resulting in the formation of hypochlorous acid (HOCl), a potent disinfectant (see Fig. 13.12).

Three major factors may contribute to wound tissue hypoxia: (1) peripheral vascular diseases garroting O_2 supply; (2) increased O_2 demand of the healing tissue; and (3) generation of ROS by way of respiratory burst and for redox signaling.¹³⁷ Other related factors, such as arterial hypoxia (e.g., pulmonary fibrosis or pneumonia, sympathetic response to pain, hypothermia, anemia caused by major blood loss, cyanotic heart disease, high altitude), may contribute to wound hypoxia as well. Depending on factors such as these, it is important to recognize that wound hypoxia may range anywhere from near anoxia to mild to modest hypoxia. In this context it is also important to appreciate that point measurements performed in the wound tissue may not provide a complete picture of the wound tissue biology because it is likely that the magnitude of wound hypoxia is not uniformly distributed throughout the affected tissue, especially in large wounds. This is most likely the case in chronic wounds presented clinically as opposed to experimental wounds, which are more controlled and homogeneous in nature. In any single problem wound presented in the clinic, it is likely that there are pockets of near anoxia as well as that of different grades of hypoxia (Fig. 13.13). As the weakest link in the chain, tissue at the near-anoxic pockets will be vulnerable to necrosis, which in turn may propagate secondary tissue damage and infection. Pockets of extreme hypoxia may be flooded with hypoxia-inducible angiogenic factors but would fail to vascularize functionally because of insufficient O_2 that is necessary

to fuel the repair process. Indeed, uncontrolled expression of VEGF and its receptors leads to insufficient skin angiogenesis.¹³⁸ Whether cells in the pockets of extreme hypoxia are O_2 -responsive is another concern. Even if such cells may have passed the point of no return in the survival curve, correction of tissue oxygenation is likely to help clean up the dead or dying tissue and replace the void with proliferating neighboring cells. Pockets of moderate or mild hypoxia are likely to be the point of origin of successful angiogenic response as long as other barriers such as infection and epigenetic alterations are kept to a minimum.

Limited supply and high demand: the oxygen imbalance

Peripheral vascular disease can affect the arteries and the veins as well as the lymph vessels. The most common and important type of peripheral vascular disease is peripheral arterial disease, or PAD, which affects about 8 million Americans. The ankle brachial pressure index represents a simple noninvasive method to detect arterial insufficiency within a limb. Arterial diseases, especially those associated with diabetes, represent a major complicating factor in wound healing. PAD is the only identifiable etiology in approximately 10% of leg ulcers. In an ischemic limb, peripheral tissues are deprived of blood supply as PAD progresses, causing tissue loss, ulcers, and gangrene.

Venous insufficiency, on the other hand, is the root cause of most leg ulcers. Chronic venous insufficiency, characterized by the retrograde flow of blood in the lower extremity, is associated with changes in the venous wall and valves generally caused by inflammatory disorders induced by venous hypertension and associated fluid shear stress. Factors causing arterial hypoxemia may also limit O_2 supply to the wound tissue. Compromised pulmonary health, loss of hepatic function, hemodialysis, anemia, altitude hypoxemia, nitroglycerin therapy, nasal packing, critical illness, pain, and hypothermia

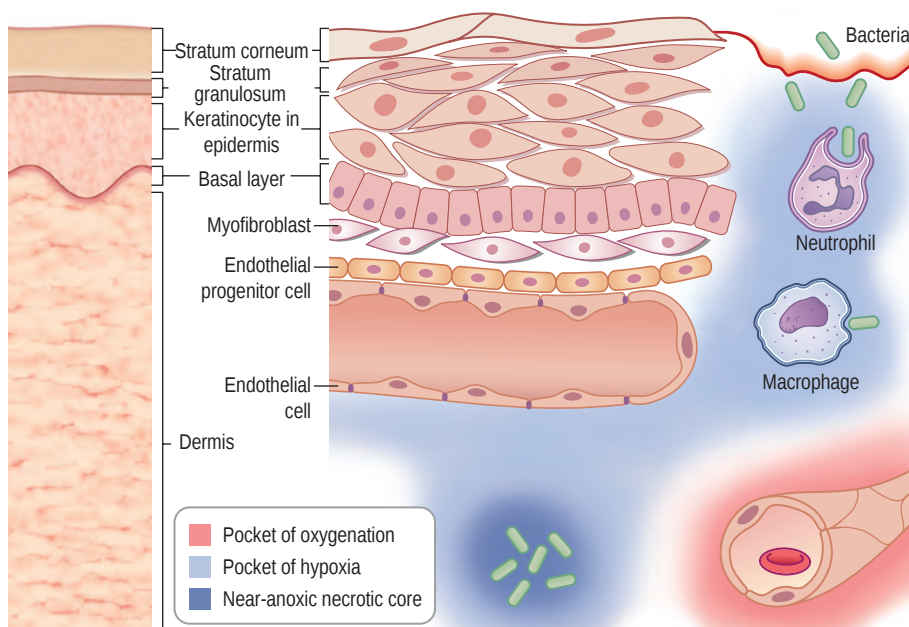


Fig. 13.13 Heterogeneous distribution of oxygen in the wound tissue: pockets of graded levels of hypoxia. Shade of blue represents graded hypoxia. Shade of red or pink represents oxygenated tissue. Tissue around each blood vessel is dark pink in shade, representing regions that are well oxygenated (oxygen-rich pockets). Bacteria and bacterial infection are presented by shades of green on the surface of the open wound.

are examples of conditions associated with arterial hypoxemia. Vasoconstricting drugs may contribute to tissue hypoxia as well.¹⁰³

Increased energy demand of the healing tissue leads to a hypermetabolic state wherein additional energy is generated from oxidative metabolism, increasing the O_2 demand of the healing tissue. Adenosine triphosphate (ATP) thus generated powers tissue repair. At the injury site, extracellular ATP may be contributed by platelets and other disintegrating cells. Extracellular ATP liberated during hypoxia or inflammation can either signal directly to purinergic receptors or, after phosphohydrolytic metabolism, can activate surface adenosine receptors. Purinergic signaling may influence numerous aspects of wound biology, including immune response, inflammation, vascular as well as epithelial biology. ATP may be immunostimulatory or vice versa, depending on extracellular concentrations as well as on expression patterns of purinergic receptors and ectoenzymes. Extracellular ATP induces receptor activation in epithelial cells. ATP, released upon epithelial injury, acts as an early signal to trigger cell responses, including an increase in heparin-binding epidermal growth factor (EGF)-like growth factor shedding, subsequent transactivation of the EGF receptor and its downstream signaling, resulting in wound healing. ATP released from the injured epithelial cells is now known also to turn on NADPH oxidases, the activity of which is critically required to produce the redox signals required for wound healing.¹³⁷ Human endothelial cells are rich in purinergic receptors and therefore responsive to extracellular ATP as well. ATP induces endothelium-dependent vasodilation. Both ATP as well as adenosine regulate smooth muscle and endothelial cell proliferation. Recognizing that hypoxia limits ATP synthesis in the ischemic wound tissue, therapeutic ATP delivery systems have been studied for their effect on wound healing. While these approaches may compensate for the deficiency of ATP *per se* in the ischemic wound tissue, they will fail to address the other essential functions of O_2 and its derivatives in wound healing, as discussed below.

Absolute requirements for O_2 arise in several points along the angiogenic sequence. For instance, all vessels require a net or sheath of ECM, mainly collagen and proteoglycans, to guide tube formation and resist the pressures of blood flow. Conditions for collagen deposition and polymerization can be created only if molecular O_2 is available to be incorporated into the structure of nascent collagen by prolyl and lysyl hydroxylases. Without the obligatory extracellular hydroxylated collagen, new capillary tubes assemble poorly and remain fragile.¹³⁹ This has a convincing clinical correlate in scurvy, i.e., ascorbate deficiency. Scurvy results from insufficient intake of ascorbate which is required for correct collagen synthesis in humans. Ascorbate is required for the post-translational hydroxylation of collagen that enables the matured collagen molecules to escape to the extracellular space and provide the necessary tensile strength. In scurvy, the collagenous sheath cannot form because, under ascorbate-deficient conditions, collagen cannot be hydroxylated. Consequently, new vessels fail to mature. Older vessels weaken and break, and wounds fail to heal. Thus, while hypoxia is a proved instigator of molecular signals for angiogenesis, it is also a proven enemy of vessel growth itself in non-tumor tissues. Collagen deposition proceeds in direct proportion to pO_2 across the entire physiologic range, from zero to hundreds

of mmHg. The K_m for O_2 for this reaction is approximately 25 and the V_{max} is approximately 250 mmHg, suggesting that new vessels cannot even approach their greatest possible rate of growth unless the wound tissue pO_2 is high.¹⁴⁰ Angiogenesis is directly proportional to pO_2 in injured tissues.^{141,142} Hypoxic wounds deposit collagen poorly and become infected easily, both of which are problems of considerable clinical significance.¹⁰³

Redox signaling

Additional high demand for oxygen is placed by a family of enzymes known as NADPH oxidases, which are known to be highly active at the wound site.¹⁴³ Recent work has identified that oxygen is not only required to disinfect wounds and fuel healing but that oxygen-dependent redox-sensitive signaling processes represent an integral component of the healing cascade.¹⁴² The widely held notion that biological free radicals are necessarily agents of destruction is now facing serious challenge.¹⁴³ Over a decade ago it was proposed that in biological systems oxidants are not necessarily always the triggers for oxidative damage and that oxidants such as H_2O_2 could actually serve as signaling messengers and drive several aspects of cellular signaling.¹⁴³ Today, that concept is much more developed and mature. Evidence supporting the role of oxidants such as H_2O_2 as signaling messengers is compelling.^{144–156}

Nitric oxide

At the wound site, NO is generated by an oxygen-dependent biosynthetic process. In the late 1970s, research was unfolding that implicated NO involvement in the process of vasodilation. By 1986, research culminated in the identification of NO as the endothelium-derived relaxing factor responsible for the maintenance of vascular tone, thus implicating NO as a potential wound-healing agent.¹⁵⁷ Maximal NO synthase activity is noted early in cutaneous wound healing, with sustained production up to 10 days after wounding. Wound macrophages represent a major source of NO production in the early phase of wound healing.¹⁵⁸ Inhibition of wound NO synthesis lowered wound collagen accumulation and wound-breaking strength, suggesting that NO synthesis is critical to wound collagen accumulation and acquisition of mechanical strength. Later it was demonstrated that wound fibroblasts are phenotypically altered during the healing process to synthesize NO, which, in turn, regulates their collagen synthetic and contractile activities.¹⁵⁹ The blockade of NO synthesis impairs cutaneous wound healing, acting in early and late phases of wound repair.¹⁶⁰ Interestingly, impaired diabetic wound healing is associated with decreased wound NO synthesis.¹⁶¹

microRNA and hypoxia response

Tissue injury is often associated with disruption of vascular supply to the injury site. Thus, the injured tissue often suffers from insufficient oxygen supply or hypoxia. Under conditions of additional underlying ischemia, hypoxia is severe and seriously limits wound healing.¹⁰³ Hypoxia induces specific miRNAs, collectively referred to as hypoxamirs.¹⁶² miRNA-210 is a classic hypoxamir. Expression of hypoxia-inducible factor 1 (HIF-1) is also controlled by specific miRNAs. In turn, HIF-1 controls the expression of hypoxamirs, which are

induced in the injured tissue.¹⁶³ Hypoxamirs are also induced by HIF-independent pathways. Although hypoxamirs generally favor angiogenesis, their metabolic and cell cycle arrest functions are in conflict with wound healing, especially in an ischemic setting. Silencing specific hypoxamirs may therefore represent a prudent approach to facilitate tissue repair. miRNA-210 represses mitochondrial respiration¹⁶⁴ and exaggerates production of undesired mitochondrial ROS.¹⁶⁴ These outcomes are not compatible with the higher energy demands associated with tissue repair. miR-210 also silences signaling via FGF¹⁶⁵ a key contributor to wound healing. The injured tissue is highly rich in ROS.¹⁶⁶ In addition, at the site of injury transition metal ions are released from a protein-bound state. Conditions such as these cause DNA damage which opposes tissue repair. DNA repair systems are therefore of key significance in enabling tissue repair. miR-210 antagonizes DNA repair.¹⁶⁶ This is another hypoxamir function that is in conflict with wound healing. Compatible with the common observation that ischemic wounds are refractory to healing response, elevated miRNA-210 in ischemic wounds attenuated keratinocyte proliferation and impaired wound closure.^{86,167}

miR regulation of angiogenesis

In 2005–2008, the first series of observations establishing key significance of miRNAs in the regulation of mammalian vascular biology came from experimental studies involved in arresting miRNA biogenesis to deplete the miRNA pools of vascular tissues and cells.¹⁶⁸ Dicer-dependent biogenesis of miRNA is required for blood vessel development during embryogenesis. Mice with endothelial cell-specific deletion of Dicer, a key enzyme supporting biogenesis of miRNAs, display defective postnatal angiogenesis. NADPH oxidase-derived ROS drive wound angiogenesis. Endothelial NADPH oxidase is subject to control by miRNAs.¹⁶⁹ Hypoxia is widely recognized as a cue that drives angiogenesis as part of an adaptive response to vascularize the oxygen-deficient host tissue. Hypoxia-induced repression of miR-200b is involved in such induction of angiogenesis by directly targeting GATA2, VEGFR2 and Ets-1.^{170,171} Various aspects of angiogenesis, such as proliferation, migration, and morphogenesis of endothelial cells, can be regulated by specific miRNAs in an endothelial-specific manner. miRNAs known to regulate angiogenesis *in vivo* are referred to as angiomiRs.¹⁷² miRNA-126 is specific to endothelial cells and regulates vascular integrity and developmental angiogenesis. Manipulating angiomiRs in the setting of tissue repair represents a new therapeutic approach that could be effective in promoting wound angiogenesis.

Impaired resolution of inflammation

The inflammation stage of wound healing is meant to be transient and self-resolving for healing to proceed normally. Temporally and spatially controlled mechanisms tightly control wound inflammation and resolution and these include removal of apoptotic neutrophils by functional macrophages. In patients with diabetes, elevated blood glucose levels results in glycosylation of phosphatidyl serine receptors on macrophages, which blocks recognition of apoptotic cells. This ineffective efferocytosis (phagocytosis of apoptotic cells) by wound macrophages results in increased production of pro-inflammatory cytokines such as TNF- α , IL-1 α , β and IL-6¹⁷³ and impaired resolution of inflammation.³⁹

miR regulation of inflammation

Disruption of miRNA biogenesis has a major impact on the overall immune system. Emerging studies indicate that miRNAs, especially miR-21, miR-146a/b, and miR-155, play a key role in regulating several hubs that orchestrate the inflammatory process.^{174,175} miRNAs have been directly implicated in the pathogenesis of inflammatory diseases such as osteoarthritis and rheumatoid arthritis. Resolvin-regulated specific miRNAs target genes involved in resolution of inflammation to establish a novel resolution circuit involving RvD1 receptor-dependent regulation of specific miRNAs.¹⁷⁶ Macrophage specific miR-21 induction was recently shown to promote an anti-inflammatory phenotype by down-regulating PTEN and PDCD4 resulting in elevated production of the anti-inflammatory cytokine IL-10.¹⁷⁷ miR-21 is efferocytosis-inducible in macrophages regulating a switch to an anti-inflammatory phenotype promoting resolution of inflammation. Furthermore, the brain-specific microRNA-124 can tame inflammation by turning off activated microglial cells and macrophages.¹⁷⁸ Of relevance to tissue repair is also the regulatory loop where cytokines, including those elicited following injury, are regulated by miRNAs, as well as regulate miRNA expression.^{179,180}

Stem cells

The regenerative potential of injured adult tissue suggests the physiological existence of cells capable of participating in the reparative process. The epithelium of the skin, the epidermis, is in a continuous equilibrium of growth and differentiation and has the remarkable capacity to self-renew completely, which relies on reservoirs of stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells (ESCs) that are isolated from the inner cell mass of blastocysts, and adult stem cells that are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenished in adult tissues. Stem cells have the property of self-renewal without differentiation and have the potential to differentiate into any type of cell. Totipotent stem cells have the ability to give rise to a whole organism due to their ability to differentiate into embryonic and extraembryonic cells. Pluripotent stem cells are derived from totipotent cells and can differentiate into all cell types but cannot give rise to a new organism (Fig. 13.14). ESCs are derived from the developing embryo, usually from the inner cell mass of a blastocyst or earlier morula stages. Lost or damaged cells can be replaced by differentiation, dedifferentiation, or transdifferentiation (Fig. 13.15). Recent advances have shown that the addition of a group of genes can not only restore pluripotency in a fully differentiated cell state (differentiation) but can also induce the cell to proliferate (dedifferentiation) or even switch to another cell type (transdifferentiation). Dedifferentiation is represented by a terminally differentiated cell reverting back to a less-differentiated stage from within its own lineage. This process allows the cell to proliferate again before redifferentiating, leading to the replacement of those cells that have been lost. Transdifferentiation is another naturally occurring mechanism that takes dedifferentiation a step further and sees cells regressing to a point where they can switch lineages, allowing them to differentiate into another cell type. Furthermore, reprogramming

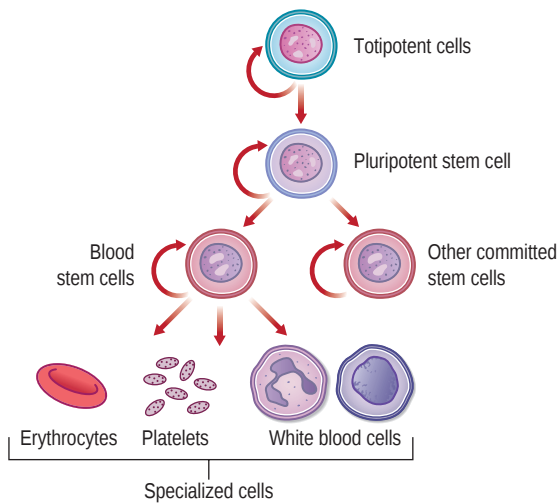


Fig. 13.14 Stem cell renewal.

aims to revert differentiated cells to pluripotency. From here, they can differentiate into almost any cell type. Although reprogramming occurs naturally during fertilization to produce totipotent cells that can differentiate into any cell type, it has not yet formally been shown to be a genuine regenerative response. Furthermore, reprogramming side-steps the necessity of using embryos for regenerative therapies by using differentiated cells taken from a patient. From a clinical perspective, this comes with the additional bonus of circumventing the immunological problems such as transplant rejection and graft-versus-host disease associated with engraftment.¹⁸¹

The bone marrow (Fig. 13.16), home of stem and progenitor cells, contributes a significant proportion of cells in the skin.

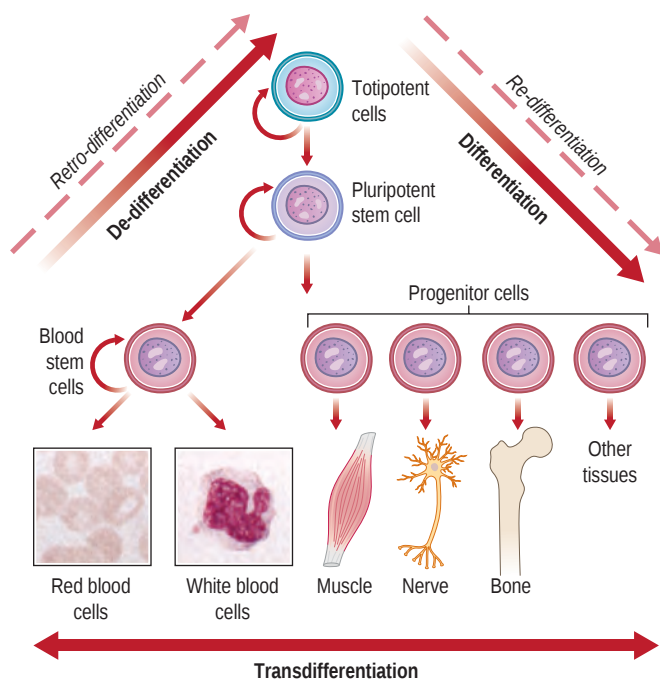


Fig. 13.15 Stem cell differentiation, dedifferentiation, and transdifferentiation

The normal skin has long been known to contain bone marrow-derived cells that are involved in host defense and inflammatory processes, including wound healing. However, recent studies demonstrate that the bone marrow contributes not only inflammatory cells, but also keratinocytes and fibroblast-shaped cells to the skin. Similar to leukocytes in trafficking, stem/progenitor cells derived from the bone marrow could home to injured tissues and participate in the repair/regeneration. Moreover, culture-expanded bone marrow-derived MSCs have been shown to promote the healing of diabetic wounds, implying a profound therapeutic potential for skin defects such as chronic wounds and burns.¹⁸²

During the inflammatory phase, leukocytes migrating to the wound site are hematopoietic cells derived from the bone marrow. In the skin the bulge of the hair follicle (Fig. 13.17) plays a role as a reservoir of stem cells. In mice it has been shown that the bulge region contains hematopoietic cells that are identical to the bone marrow-derived cells and also to those found in fetal circulation.¹⁸³ Moreover this region also serves as a reservoir for precursors of mast cells. Discovery of these epidermal stem cells in the hair follicle bulge led to the hypothesis that these cells are necessary for both epidermal renewal as well as wound healing.^{184,185} It was shown that cells from the bulge do not contribute to epidermal regeneration;

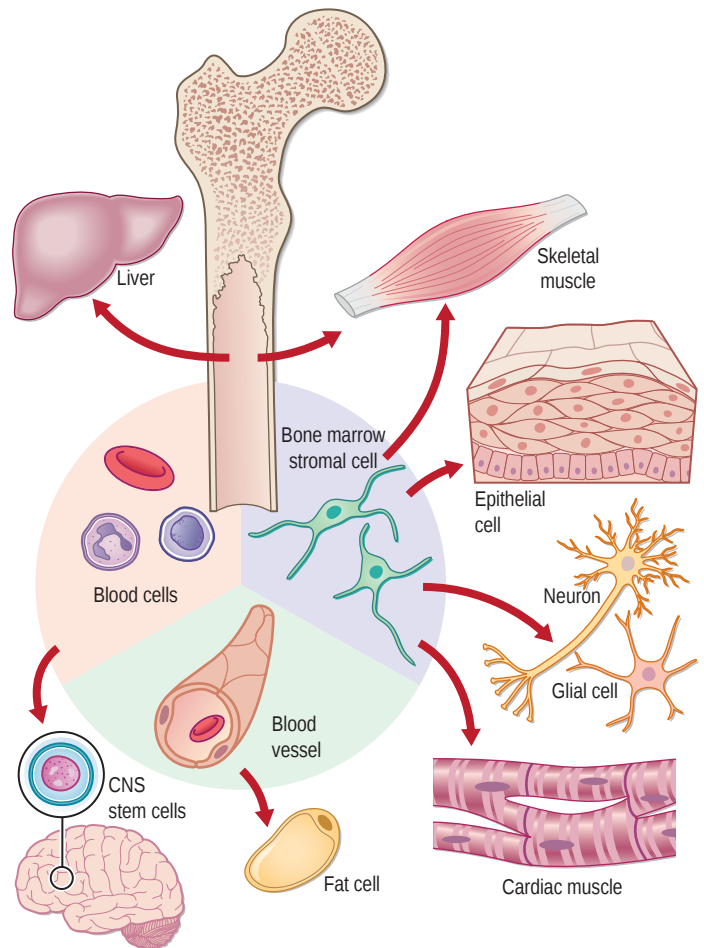


Fig. 13.16 Bone marrow stem cells. CNS, central nervous system.

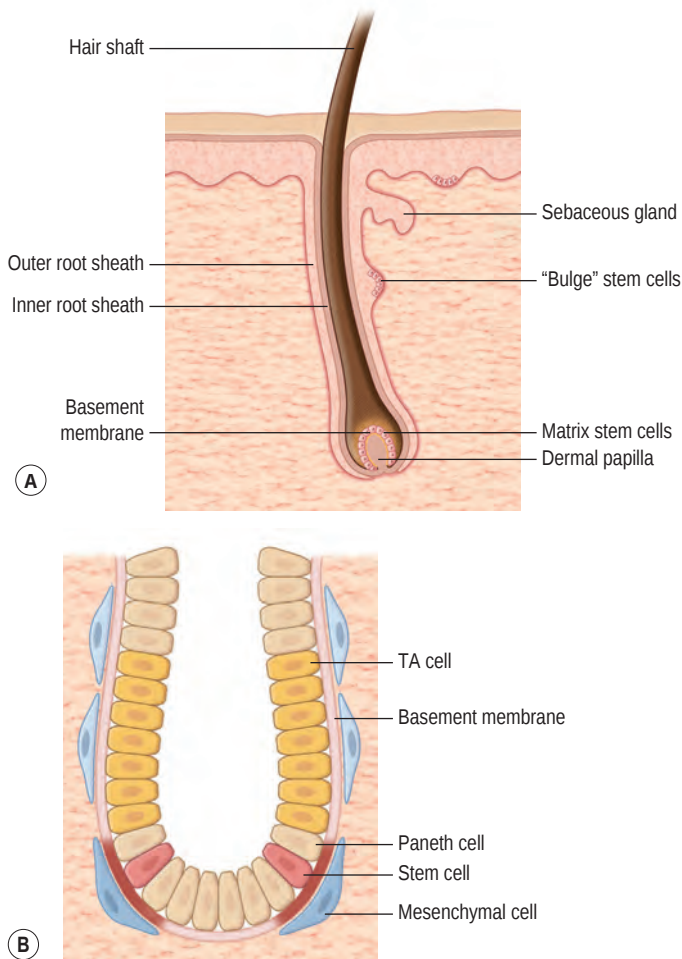


Fig. 13.17 Stem cells in the epidermis. Hair follicles act as reservoirs of stem cells in the skin. **(A)** Cross-sectional view of a hair follicle. The matrix stem cells differentiate into various parts of the hair while the long-term stem cells are present in the bulge region. The stem cells from the bulge maintain the sebaceous gland and epidermal stem cells. **(B)** A mammalian gut crypt. Stem cells are located at the basal region with the Paneth cells. The transit amplifying (TA) cells are stem cell progeny which move upwards and differentiate.

however, upon injury cells from the bulge are recruited into the epidermis and migrate in a linear manner toward the center of the wound.¹⁸⁵ These cells were noted to be transient, living only for a few weeks, thus representing an acute response to injury.

There are two main branches of stem cells in the bone marrow, including hematopoietic stem cells (HSCs) and MSCs. Adult bone marrow-derived HSCs have long been recognized as a precursor to all blood cell lineages, including erythrocytes, platelets, and white blood cells. Additionally, HSCs may also give rise to fibrocytes and endothelial progenitor cells. Circulating endothelial precursor cells play a role in neovascularization which is essential for healing.^{186,187} Bone marrow-derived stem cells also contribute to the deposition of collagen III in the wound¹⁸⁸ and differentiate into fibroblasts,¹⁸⁹ keratinocytes,¹⁹⁰ and fibrocytes.¹⁹¹ Bone marrow-derived MSCs, which are also referred to as bone marrow mesenchymal stromal cells or marrow stromal cells, are self-renewing and expandable stem cells. Although present as a rare cell population in the bone marrow,

representing about 0.001–0.01% of the nucleated cells, about 10-fold less abundant than HSCs, MSCs are expandable in culture and multipotent, capable of differentiating into several cell types.

Because of their properties of regeneration and differentiation, the use of stem cells to heal problem wounds has long been of interest. Indeed, autologous bone marrow aspirates and cultured cells were helpful in healing chronic wounds.¹⁹² In the case of burn wounds, bone marrow-derived stem cell treatment shows promise as well.¹⁹³ Another major source of adult stem cells is adipose tissue.¹⁹⁴ The capability of adipose-derived adult stem cells to differentiate into bone, muscle, fat, or cartilage, or into cells of mesenchymal lineage, makes them a prime target for therapeutic use. It has been shown that adult stem cells enhanced wound healing in a murine model.^{195,196} However, a caveat to the indiscriminate use of autologous stem cell therapy in wound healing, particularly in the diabetic population, was revealed in a recent study that demonstrated that diabetic adipose-derived stem cells (ASCs) are compromised in their ability to initiate vascularization and ineffective in wound healing.¹⁹⁷

Hair follicles are an integral part of mammalian skin where they help the epidermis to maintain the body's protective barrier against its external environment. With rare exceptions (such as palms and eyelids), hair follicles are present all over the skin and play an important role in physiological tissue renewal and regeneration after injury. Hair follicles represent an autonomous miniorgan, which provides an excellent model system for studying the biology of adult stem cells.¹⁹⁸ There are obvious differences between human and mouse skin, yet the knowledge gained from lineage-tracing experiments in mice has greatly expanded our understanding of the cellular behavior of the different keratinocyte populations during physiological and injury-induced tissue regeneration. As in most of the body's organs, the skin experiences constant renewal. The upper keratinized layer of the interfollicular epidermis, which consists of terminally differentiated cells, is shed and replaced by cells originating from the actively proliferating layer beneath. In contrast, hair follicles undergo cycles of growth (anagen) and rest (telogen). The potential for proliferation to sustain the lifelong replenishment of normal cell loss and to repair occasional tissue damage lies within the population of epidermal stem cells. The hair follicle bulge harbors stem cells that may help in renewal and repair of the skin. The term "bulge", originally called "*der Wulst*", was introduced in 1903 by a German morphologist, P. Stöhr, to describe an eminent structure at the site of attachment of the arrector pili muscle in human hair follicles.¹⁹⁹ Similar to many other somatic stem cells, bulge cells are slow-cycling in nature. This feature has permitted their initial identification and isolation as label-retaining cells that can retain a pulse of nucleotide label following a long chase period and is frequently regarded as a defining characteristic of the hair follicle stem cell. In addition, the availability of several immunohistochemical markers, including keratin-15 and CD34, that specifically label murine follicular stem cells has given researchers the ability to examine carefully the signals required for adult stem cell activation and renewal. We now know that the bulge serves as a repository of long-lived multipotent stem cells, imparted with the capacity to differentiate into all cell types that constitute the lower cyclic portion of the hair follicle, as well as the interfollicular epidermis during wound repair.^{198–200}

Although research into the use of stem cells for regenerative medicine is on a steep upward slope, clinical success has not been as forthcoming. This has been primarily attributed to a lack of information on the basic biology of stem cells, which remains insufficient to justify clinical studies. Since most clinical protocols use intravenous application of MSCs, it has become important to understand their trafficking in the blood stream. Moreover, since relatively little is known where the transplanted MSCs might locate, a better understanding of involved homing mechanisms will likely shed light on how MSCs exert their therapeutic effects. For instance, it is unclear whether mechanisms used at injured sites are location-specific or whether this recruitment can be modulated for therapeutic purposes. In addition, it has recently been suggested that platelets may play an important role in stem cell recruitment to sites of injury. A better understanding of the mechanisms used by stem cells during tissue homing would allow us to develop strategies to improve recruitment of these rare cells.²⁰¹

Induced pluripotent stem cells

Pluripotent stem cells possess the unique property of differentiating into all other cell types of the human body. The discovery of induced pluripotent stem cells (iPSCs) in 2006 has opened up new avenues in clinical medicine.^{202,203} Recent breakthrough studies using a combination of four factors to reprogram human somatic cells into pluripotent stem cells without using embryos or eggs have led to an important revolution in stem cell research. It is now possible to convert somatic cells, such as skin fibroblasts and B lymphocytes, into pluripotent stem cells that closely resemble ESCs. Recently, functional neurons, cardiomyocytes, pancreatic islet cells, hepatocytes, and retinal cells have been derived from human iPSCs, thus reconfirming the pluripotency and differentiation capacity of these cells. These findings further open up the possibility of using iPSCs in cell replacement therapy for various disorders, including chronic wounds.

miRNA regulation of stem cells

Endogenous miRNA-binding sites have been identified in murine embryonic stem cells (ESCs). miRNAs govern ESC function by serving as control hubs managing regulatory networks. A central importance of such governance is highlighted by the observation that ESCs lacking miRNAs lose their “stemness”. ESCs with deficient miRNA biogenesis systems switch to a mode of ongoing cell division. They do not differentiate on demand because of failure to turn off the pluripotency regulatory program.²⁰⁴ miRNAs conduct the orchestra of critical gene regulatory networks controlled by pluripotency factors within stem cells. Individual miRNA-dependent pathways that promote the reprogramming of somatic cells into iPSCs have now been identified. Manipulation of specific cellular miRNAs helps enhance reprogramming of somatic cells to an ESC-like phenotype, helping to generate iPSCs.²⁰⁵ Expression of miRNAs is also subject to control by epigenetic factors.^{83,206} Such control influences the balance between proliferation and differentiation of stem cells. In executing such control, the miRNA element of epigenetics cross-talks with changes in chromatin structure as well as with changes in DNA methylation. Collectively, this provides for a mechanism by which the tissue injury

microenvironment can influence miRNA-dependent reparative and regenerative processes.

Non-invasive wound measurements

Laser speckle flowmetry

Functional assessment of wound vascularization is made possible by the application of the laser speckle imaging technology which provides dynamic response and spatial resolution resulting in both real-time graphs and video recordings of the area of interest. The speckled patterns (dark and bright areas) generated by the instrument reflect the degree of movement in the area under consideration. Blurring in the speckle patterns indicates motion of the particles in the blood. Blurred (in motion) areas therefore can be contrasted from those without blurring (no motion) and color coded to generate perfusion maps. It is therefore a powerful approach for blood perfusion imaging. Laser speckle imaging has been used for the assessment of spatio-temporal hemodynamic changes during excisional and burn wound healing.^{207–209} Shown in Fig. 13.18 are longitudinal measurements of perfusion changes in the entire wound area as healing progressed for a period of six weeks. The increased perfusion along the wound edge during early stages of wound healing reflect initial vasodilation (day 3) followed by neovascularization, which gradually moves towards the wound bed (days 21–42) as resolution occurs along the edge.

High resolution harmonics ultrasound imaging

Modern ultrasound systems have been applied to vascular imaging, visualizing 3D structures in motion and measuring the stiffness of tissues. For the skin, higher spatial resolution can be obtained with low frequency sound waves which allow the differentiation of the epidermis, dermis and subcutaneous fat and the muscle layers. Using the color Doppler imaging (CDI) application, longitudinal imaging of functional blood flow parameters in a gated peripheral feeder artery supplying the wound site were visualized for the first time indicating a bimodal pattern of arterial hemodynamics throughout the process of wound healing (Fig. 13.19). Additionally, B-mode imaging and elastography of wound areas have provided 3D visualization and measurement of wound depth, cavities/tunnels, scar formation and mechanical features of the wound that would otherwise go undetected by current clinical standards.²⁰⁹

Transepidermal water loss (TEWL)

The TEWL measurement is a reliable indicator of skin barrier function²¹⁰ and is an important parameter to consider for skin health and function. TEWL measurements indicate the quantity of water that passes from inside a body through the epidermal layer to the external environment via diffusion and evaporation processes. These can be influenced by humidity, temperature, hydration status of the skin, etc., and should be interpreted cautiously. Increased TEWL measurements could indicate loss or impairment of barrier function indicating that such skin is not only vulnerable to loss of

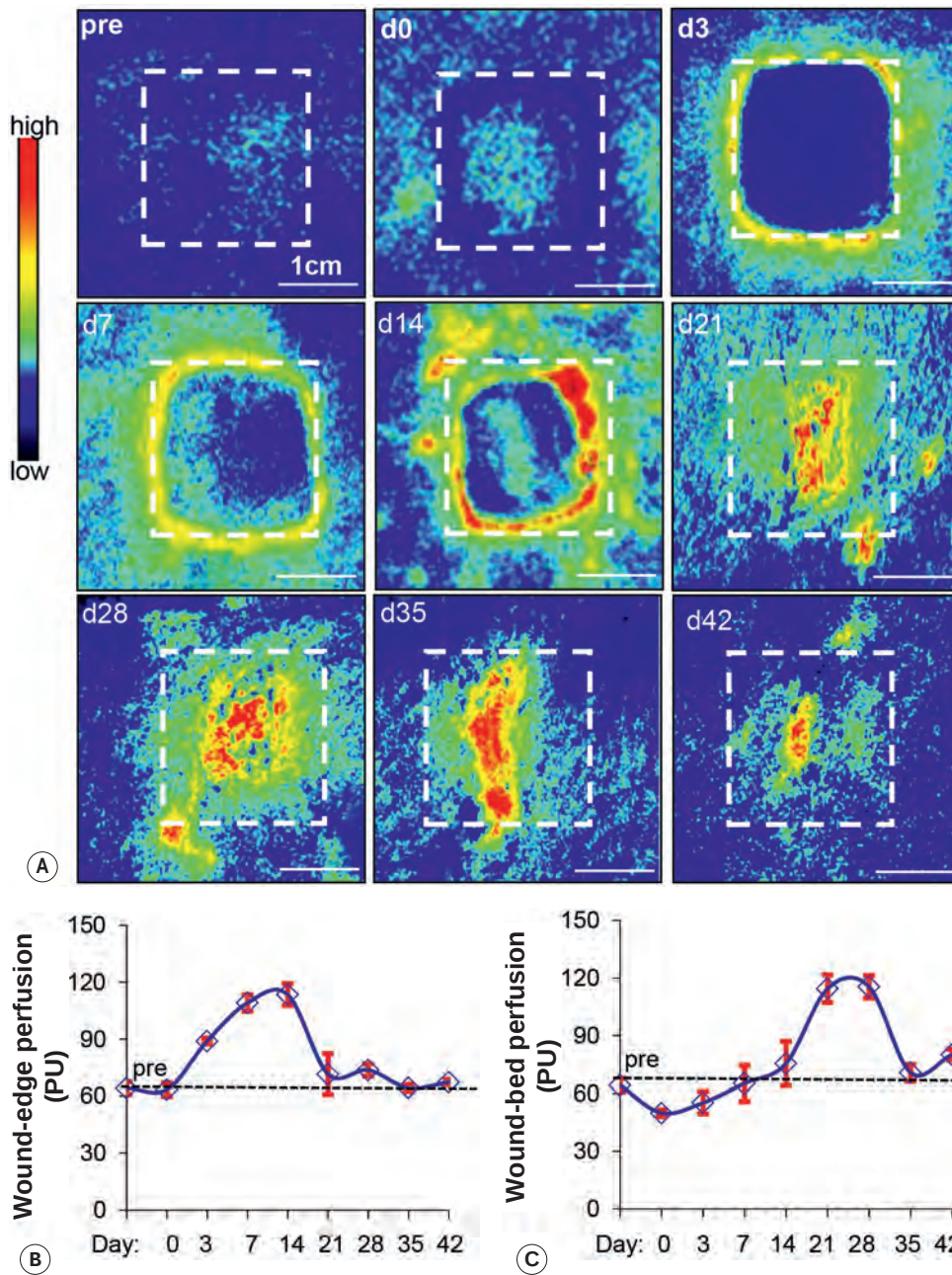


Fig. 13.18 Laser speckle perfusion imaging shows dynamic changes in wound-site blood flow over time. (Reproduced from Gnyawali S, Barki KG, Mathew-Steiner SS, et al. High-resolution harmonics ultrasound imaging for non-invasive characterization of wound healing in a pre-clinical swine model. Plos One, 2015;10:e0122327.)

moisture but is now a portal of entry for microbes and other irritants. Recent evidence from preclinical studies emphasizes the need for functional assessments of wound closure using measurements such as TEWL. Biofilm-infected wounds that appeared visually closed showed high TEWL readings indicating functional barrier failure which was then linked to the downregulation of critical cellular tight junction proteins (ZO-1 and ZO-2) by biofilm-induced microRNAs (miR-146a and miR-106b).¹¹³

Hyperspectral imaging

This technique is a non-invasive, non-destructive, chemical-free assessment that provides maps of oxygenated tissue

allowing qualitative and quantitative measurements with high spectral resolution. A combination of a highly sensitive charge-coupled device (CCD) and infrared (IR) cameras detect dynamic changes of tissue hemoglobin concentration and temperature distribution in response to vascular occlusion and reperfusion resulting in oxygenation maps. The OxyVu-2 software is used to perform imaging analysis that allows post-processing of the hyperspectral images for tissue oxygenation (StO_2). This imaging method has been used to characterize the hypoxia component of tissue ischemia in a mouse model¹⁶⁷ and in combination with laser speckle and thermal imaging modalities, it has been applied to studies on normal human subjects following post-occlusive, reactive hyperemia procedures.²¹¹

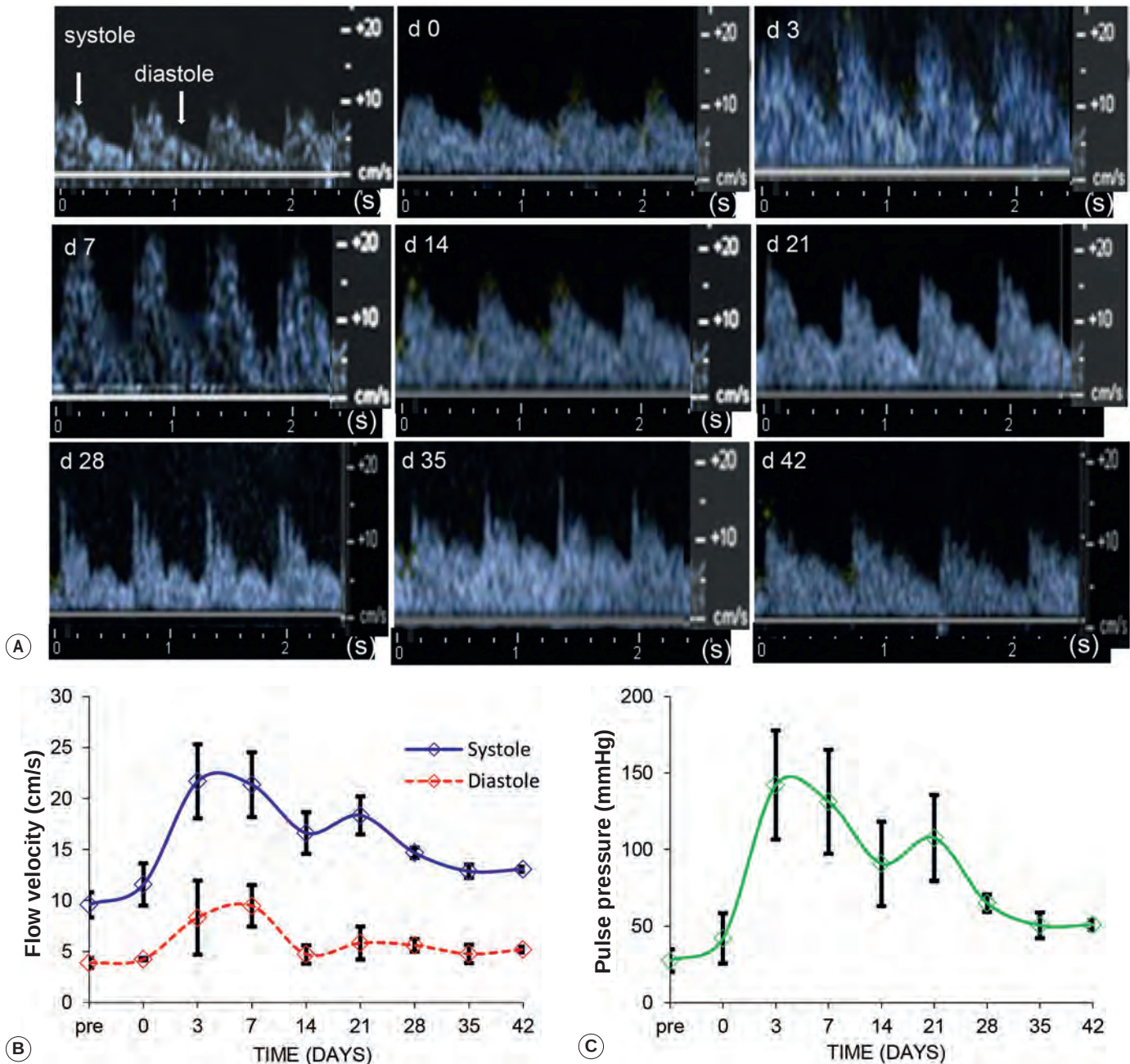


Fig. 13.19 Ultrasound measurement of pulse pressure indicates enhanced blood flow via feeder artery supplying the edge of the wound. (Reproduced from Gnyawali S, Barki KG, Mathew-Steiner SS, et al. High-resolution harmonics ultrasound imaging for non-invasive characterization of wound healing in a pre-clinical swine model. Plos One, 2015;10:e0122327.)

Near infrared thermal imaging

IR thermography is a technique suited to non-invasive imaging of inflammation in tissue. A thermal imaging camera, Thermovision™ model A40, is used to capture and record thermal distributions and variations in real-time, *in vivo*, as an indicator of inflammation. The sensitivity of the camera allows the detection of changes as small as 0.02°C. The ResearchIR software allows high speed recording and advanced post-processing of fast-changing thermal

events. Thermography has been applied to diabetic foot and pressure ulcers to identify latent inflammation. The increased temperature measured in these types of wounds could indicate inflammation or other factors that impair wound healing. In combination with laser speckle and hyperspectral imaging, thermographic imaging has been used in a multimodal imaging format to continuously monitor the wound-healing process in a clinical trial, demonstrating its clinical applicability in wound-healing assessment.²¹¹

Clinical wound management

Clinical vignette – acute wounds and elective surgical patients

Diagnosis/patient presentation

The preoperative evaluation should include a thorough medical history, a social history that includes determining who or how wound care or postoperative care will be provided, pulse exam if the wound is on the lower extremity, and a nutritional assessment. If the patient is diabetic, then hemoglobin A1c should be checked. Protein synthesis, especially collagen, is essential to healing and pre-albumin is a good basic indicator of protein synthesis capacity. However, it is an acute phase reactant, so it will be depressed during concomitant episodes of sepsis or other generalized inflammatory response. To address this, pre-albumin levels can be followed serially as often as 2 times per week (half-life is 2 days compared to albumin with a half-life of 20 days) as it should rise as the inflammatory state subsides or with initiation of protein supplementation. The steady state pre-albumin value is an indicator of the patient's nutritional status and has been shown to correlate with clinical outcomes.²¹²

Patient selection

Every surgical patient is a wound patient once the scalpel cuts the skin. The prudent surgeon will optimize conditions for good wound healing and surgical outcomes by preparing the patient *and the wound bed* for surgical closure.

Treatment (wound-healing specific)

- If protein malnutrition is present it is reasonable to assume other nutritional factors are also depleted. Multivitamin and essential element supplementation should be included in the nutritional optimization plan.
- For patients on a chronic glucocorticoid medication regimen, vitamin A supplementation can overcome some of the detrimental effects of these steroids on wound healing.²¹³ It can be given for 2 weeks typically at 10 000 IU per day and should be started immediately postoperatively for surgical patients.
- Optimize glucose control depending on results of hemoglobin A1c or blood glucose monitoring. Elective cases should be postponed in patients with poorly controlled diabetes as there is abundant literature indicating the poor surgical and wound-healing outcomes associated with poor glucose control.
- Debridement must be adequate to remove all devitalized or infected tissue otherwise it delays progression from the inflammatory to the proliferative phase of wound healing (see section on inflammatory phase).
- All open wounds must be examined by probing with a finger and if not possible then a cotton tip applicator to make sure there are no foreign bodies, underlying bony injuries, or fistulous tracts.
- Wound beds must be free of infection prior to closure or have ongoing treatment for infection at the time of surgical closure to prevent wound recurrence. Weekly wound debridement is a good clinical practice to achieve this objective.
- Optimize perioperative tissue perfusion conditions for good wound healing outcomes* – the following recommendations are supported by level 1 evidence and are especially useful for flap patients.
 - Maintain normothermia ($\geq 36^{\circ}\text{C}$) intraoperatively – significantly decreases the rate of postoperative wound infection²¹⁴
 - Provide adequate fluid resuscitation intraoperatively and postoperatively – increases tissue oxygenation and capillary blood flow.²¹⁵ For open laparotomy cases patients were given 16–18 ml/kg per hour during surgery.
 - Perioperative administration of supplemental oxygen, such as 0.8 fraction of inspired oxygen (FiO_2) given intraoperatively and 2 hours postoperatively, is sufficient to significantly decrease postoperative infection rates, length of stay, and mortality. However, *these results can only be achieved when the patient is normothermic and adequately perfused/intravascularly replete.*²¹⁶

Outcomes/prognosis/complications

- The expected outcome for a wound that heals by primary intent is that the incision is sealed by 24–48 hours because of fibrin deposition in the wound. At that point the wound progresses to the proliferative phase of healing.
- The prognosis for an uncomplicated wound that heals by primary intent is that the incision will acquire tensile strength at the following rate: 10% at 2 weeks, 30% at 4 weeks and 80% at 6 weeks compared to intact normal skin. Maximal tensile strength of the incision is achieved at 6 weeks after closure and thus never achieves the same tensile strength as intact skin.²¹⁷
- Infection is a common and highly undesirable complication for wounds or surgical procedures. The expected rate of surgical site infection²¹⁸ can be roughly estimated using the wound classification as defined by the Centers for Disease Control.
 - Class I/Clean – An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. **Expected infection rate: 1–2%**
 - Class II/Clean-contaminated – An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered. **Expected infection rate: 3%**
 - Class III/Contaminated – Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique (e.g., open cardiac massage) or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category. **Expected infection rate: 6%**
 - Class IV/Dirty-infected – Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation. **Expected infection rate: 7–13%**
- Risk factors for surgical site infection²¹⁹ include:
 - Patient characteristics
 - Age
 - Obesity
 - Smoking
 - Diabetes
 - Nutritional status
 - Colonization with microorganisms
 - Altered immune response
 - Co-existing infections at a remote body site
 - Length of preoperative stay
 - ≥ 3 diagnoses at the time of discharge

- b. Operative characteristics
 - i. Abdominal operation
 - ii. Operation lasting longer than 2 hours
 - iii. Wound class III or IV
- c. Surgical technique
 - i. Poor hemostasis
 - ii. Failure to obliterate dead space
 - iii. Tissue trauma
- 5. Incision dehiscence/wound recurrence – occult biofilm infection (see [miR regulation of skin barrier functions](#))
 - a. Determination of wound closure – the skin as an organ has 3 primary functions: thermoregulation, prevention of evaporative water loss, and to serve as a barrier to infections. Wounds that have occult biofilm infection will appear closed, but the skin will be functionally defective with elevated levels of transepidermal water loss (TEWL – see non-invasive imaging modalities). Channels in the cells that let water out of the skin will also let bacteria into the skin. The finding of elevated TEWL is most likely to occur in the clinical setting of surgical closure of wounds with pre-existing biofilm infection.
 - b. Unrecognized soft tissue or bony infection, especially occult biofilm infection, is a suspected cause for a significant number of flap dehiscence/wound recurrence outcomes. Biofilm-producing bacteria express high levels of ceramidase that enzymatically digests skin lipids.²²⁰ Adjunctive therapy with topical antibiotics or biofilm-inhibiting dressings (see section on [Electroceuticals](#)) at the time of debridement along with systemic antibiotics may mitigate the risk for postoperative biofilm infection.
 - c. Measurement of C-reactive protein and erythrocyte sedimentation rate can be used to screen for osteomyelitis preoperatively (if elevated, confirm diagnosis with imaging studies). Serial measurements with an anticipated decrease in these inflammatory markers can be used to monitor response to therapy.

*Hints and tips – One way to optimize postoperative conditions for successful flap surgery is using the following regimen: maintenance IV at 2 ml/kg/hr and 4 liter oxygen per nasal cannula for 24 hours postoperatively. Keep the room warm (if in a single room) with the temperature set at 80°F (26.6°C) or keep patient covered and warm until discharge. This promotes vasodilation, optimal perfusion and O₂ delivery to the flap. It will also increase collagen deposition for wound healing and decrease risk for infection.

Clinical vignette – diabetic foot ulcer (DFU)

Diagnosis/patient presentation

Patients with diabetic foot ulcers commonly present with a classic triad of clinical findings: ischemia, neuropathy and foot deformity. The ulcers are frequently initiated by local trauma where the patient cannot sense the injurious event because of underlying sensory neuropathy. For this reason diabetics are instructed never to go barefoot. Pressure from poorly fitting footwear because of foot deformity is another common initiating event. An early sign of pressure on the foot is the development of a callus, which should be interpreted as impending foot ulceration if there is no intervention to off-load the pressure. Development of foot deformity is attributable to several factors. Neuropathy contributes to the development of Charcot changes in the midfoot with osteopenia, fractures/dislocations, and collapse of the arch. The metatarsal heads become prominent with extension of the toes at the metatarsal phalangeal joints because of motor neuropathy of the intrinsic foot muscles ([Fig. 13.20](#)). Elevated glucose levels cause glycosylation of the Achilles tendon that limits excursion. There is decreased range of motion with foot dorsiflexion, which affects gait mechanics. Normally there is a heel strike and then rolling up onto the ball of the foot as a person progresses through their stride. The loss of foot dorsiflexion results in a foot strike that is more like a peg with the forefoot absorbing more of the impact during the stride than normal thereby leading to forefoot ulceration. The risk for forefoot ulceration is increased when metatarsal heads are prominent. The combination of elevated glucose and diseased vaso nervorum is thought to be responsible for the motor and sensory neuropathies that are observed in these patients, but it also affects autonomic nerves. There is loss of vasomotor regulation, arteriovenous shunting, and when combined with microangiopathy (thickened basement membrane, thrombosis) results in ischemia at the areas of tissue injury. This means that a patient can present with a pink foot with palpable pulses and a wound that is actually not well perfused.

Patient selection

Prior to any non-emergent surgical procedure, patients should have hemoglobin A1c checked and glucose control optimized. All patients need a thorough vascular exam to determine whether there is adequate blood flow to the foot to support wound healing prior to any bedside debridement or non-emergent operative surgical procedures. Patients with inadequate blood flow need revascularization to achieve a closed wound.

Treatment

1. Deformity – off-loading interventions are an essential part of any treatment plan and can include
 - a. Complete non-weight bearing – e.g. crutches or wheelchair
 - b. Total contact casting – not removable and changed weekly by a healthcare professional
 - c. Removable cast walker – e.g., walking boot, cast shoe
 - d. Modified footwear – required to heal and prevent ulcerations in patients with foot deformity, refer to podiatrist for evaluation
2. Infection – risk for infection increases the longer the wound is open
 - a. Glucose control is essential – poor glycemic control results in impaired macrophage function, inability to resolve inflammation (see section on [resolution of inflammation](#)) and an open wound stalled in the inflammatory phase of healing
 - b. Osteomyelitis
 - i. If bone is exposed, the likelihood of infection/osteomyelitis is 80%
 - ii. Infected bone should be debrided
 - c. Biofilm – bacteria in a biofilm state are tightly adherent to the wound surface
 - i. If bone is exposed the bacteria will adhere to bone causing osteomyelitis that cannot be treated with antibiotics alone. Surgical debridement along with antibiotics is required to eradicate the infection.*
 - ii. The presence of biofilm will result in a chronic open wound – debridement disrupts biofilm, but it will recur,¹¹³ therefore good clinical practice is weekly debridement
3. Ischemia – there must be adequate blood flow to support wound healing
 - a. Diagnosis
 - i. Ankle-brachial index with pulse waveforms – must include pulse waveforms as index values can be falsely elevated because of atherosclerotic disease of the arteries (ABI >1.2)
 - ii. Toe-brachial index – detects vascular obstruction distal to the ankle, should be used for all ulcers located on the

foot and should include pulse waveforms. Adequate perfusion is a TBI >0.6

- iii. Transcutaneous oxygen measurement (TcOM) – closest measurement of tissue perfusion near wound. It gives absolute values of tissue oxygenation in mmHg, so results are easy to interpret. Adequate perfusion is ≥ 30 mmHg
- iv. Skin perfusion pressure – occludes blood flow and measures the opening pressure at which perfusion first returns to the cutaneous microcirculation after controlled release of the occlusion. It combines the use of a laser Doppler and a pressure cuff. Adequate perfusion is ≥ 30 mmHg
- v. Angiography – may miss occlusion of perforators off axial vessels in the lower extremity
- vi. Laser speckle – provides a dynamic image of blood flow

b. Treatment

- i. Surgical revascularization
- ii. Stenting – for smaller vessels below the knee just need patency long enough to get wound healed
- iii. Hyperbaric oxygen (HBO) – can be used for patients who are not candidates for surgical revascularization or in preparation for flap or graft

4. Surgical interventions

- a. Weekly bedside debridement is associated with improved healing outcomes²²¹
- b. Achilles tendon lengthening will promote healing of forefoot ulcers in patients with less than 10 degrees of passive ankle dorsiflexion with the knee flexed and extended^{222,223}
- c. Successful surgical closure with a flap or graft can be achieved when the wound bed is free from infection, the wounded area on the foot is appropriately off-loaded, there is adequate blood supply to support healing, and the patient is nutritionally replete with good glucose control.

5. Advanced therapies

- a. HBO – stimulates angiogenesis and eradicates infection from specific pathogens. Patients with DFU that qualify for HBO treatment are Wagner grade 3 or higher AND have failed to improve after at least 30 days of standard therapy. Meta-analysis indicates that for every 4 patients treated with HBO, 1 major amputation, i.e. below-knee or above-knee amputation, would be prevented.²²⁴
- b. Engineered skin – e.g. Apligraf® or Dermagraft®
- c. Extracellular matrix products – e.g. Promogran Prisma®
- d. Growth factors
 - i. Recombinant platelet derived growth factor-BB – Regranex™ is the FDA-approved version of the growth factor indicated for use in diabetic foot ulcers. However, it was given a boxed warning by the FDA in 2008 for an increased risk of malignancies observed distant to the site of application in patients treated with 3 or more tubes. It is no longer used and serves as a reminder of the potential off-target effects of growth factors.
 - ii. Autologous platelet gel (APG) is a cell-based therapy that delivers growth factors and cytokines to the wound through topical application to the wound bed. The data

is mixed regarding APG efficacy and level 1 evidence is not available. The challenge with APGs is titrating the level of growth factor and cytokine release to have it fall within a therapeutic range.

Outcomes/prognosis/complications

1. Validated diabetes foot ulcer severity scores^{225,226}

- a. Wagner grade
 - i. Grade 0: No open lesions; may have deformity or cellulitis
 - ii. Grade 1: Superficial ulcer, partial or full-thickness
 - iii. Grade 2: Ulcer extension to ligament, tendon, joint capsule, or deep fascia; no abscess or osteomyelitis
 - iv. Grade 3: Deep ulcer with abscess, osteomyelitis, tendonitis or joint sepsis
 - v. Grade 4: Gangrene localized to portion of forefoot or heel
 - vi. Grade 5: Total foot gangrene
- b. University of Texas – stage is the more sensitive prognostic indicator
 - i. Stages
 - I. Stage A: No infection or ischemia
 - II. Stage B: Infection present
 - III. Stage C: Ischemia present
 - IV. Stage D: Infection and ischemia present
 - ii. Grading
 - I. Grade 0: Epithelialized wound
 - II. Grade 1: Superficial wound
 - III. Grade 2: Wound penetrates to tendon or capsule
 - IV. Grade 3: Wound penetrates to bone or joint

2. Prognosis

- a. Correlates with ulcer severity – worse prognosis, e.g. time to heal and risk for amputation, with increasing severity
- b. The average diabetic foot ulcer is open for 12 months
- c. Presence of end stage renal disease (ESRD) worsens prognosis

3. Complications – amputation is the feared complication. The prognosis for patients getting amputations is worse than many types of cancer. Amputation is considered preventable by CMS if patients receive good foot care and it is used as a quality indicator for population-based healthcare.

- a. 80% of amputations in patients with diabetes mellitus are preceded by foot ulceration
- b. Survival rate after below-knee amputation
 - i. Without ESRD: 1 year = 72.5% and 5 year = 35%
 - ii. With ESRD: 1 year = 54.6% and 5 year = 16%
- c. Survival rates for diabetic patients after above knee amputation
 - i. Without ESRD: 1 year = 48% and 5 year = 16%
 - ii. With ESRD: 1 year = 26.8% and 5 year = 8.2%

*Hints and tips – Use resorbable antibiotic-impregnated beads in the wound after resection of infected bone to achieve a sustained release of high levels of antibiotics directly at the site to prevent recurrent biofilm infection, osteomyelitis and flap dehiscence (Fig. 13.21). A common approach is to use 1 g vancomycin and 1.2 g tobramycin mixed in with the bead material (Stimulan®, Novartis). Serum levels should be checked postoperatively and if levels are significantly elevated irrigate through a closed suction drain to get the beads to dissolve.

Clinical vignette – venous leg ulcer (VLU)**Diagnosis/ patient presentation**

VLU are present in 1% of the population.⁵ Important antecedent events are a history of major lower extremity trauma, deep vein thrombosis (DVT), varicose veins, and obesity. VLU are caused by incompetence of the venous valves in the leg resulting in a static column of blood pooling in the lower extremity. The venous hypertension causes an increase in the number of dermal capillaries in the skin with increased capillary pressure and increased capillary permeability. This leads to extravasation and perivascular deposition of blood and fibrinogen/fibrin. The fibrin barrier prevents oxygen diffusion out of the capillary beds into the surrounding soft tissues resulting in ischemia, lipodermatosclerosis, and ulceration.²²⁷ Tissue affected by lipodermatosclerosis is stiff, friable, ischemic, and heals poorly. Patients will complain of aching, itching, heaviness, tightness, pain or muscle cramps. The ulcers are superficial with irregular borders, usually located near the medial malleolus with surrounding hemosiderin deposits and lipodermatosclerosis. There may be copious drainage from the ulcers as well. The diagnosis of VLU can be confirmed with non-invasive vascular studies. Duplex ultrasound with proximal compression of the vein or Valsalva maneuver to look for venous reflux is the gold standard for diagnosis with plethysmography as an alternative method if reflux studies are inconclusive. Venography, helical venous CT and MR have also been used to establish the diagnosis. Patients with VLU have an increased risk for thrombotic events, especially with a personal or family history of thrombotic events, early onset VLU prior to age 50, and recurrent or recalcitrant VLU.^{228,229}

Patient selection

All patients must be evaluated for peripheral artery disease, which is present in at least 30% of patients with VLU. The presence of peripheral artery disease changes the management of patients with VLU. The Society for Vascular Surgeons and American Venous Forum recommend laboratory evaluation for thrombophilia in patients with a history of chronic or recurrent VLU.²³⁰

Treatment

It is important to remember the VLU is the symptom and the disease is venous valvular incompetence. Treatments directed toward the ulcer will not cure the disease.

1. Compression is the mainstay of therapy – patients with VLU should understand it will be needed *constantly and forever*. Compression cannot be used when the patient has significant peripheral artery disease (ABI <0.7 or >1.2). A toe–brachial index >0.6 or a transcutaneous oxygen measurement >30 mmHg indicates adequate arterial flow to use compression therapy.
 - a. Graduated pressure compression stockings should be worn daily when the patient does not have a VLU.
 - b. 4-layer compression wraps changed weekly can be used when VLU is present. A long-lasting topical antimicrobial dressing can be placed on the ulcer beneath the compression wrap if the VLU is infected.

- c. Intermittent pneumatic compression stockings can be used by persons who cannot wear compression stockings.
2. Elevate extremity – keep affected legs elevated when possible and especially when not using compression, as edema limits oxygen diffusion to the tissues.
3. Increase calf muscle pump functions – targeted exercises can help.
4. Surgical interventions
 - a. To treat valvular incompetence – only effective when disease is limited to superficial venous system, should not be used when deep venous disease, DVT, or obstruction are present as it can make ulcers more recalcitrant
 - i. Subfascial endoscopic perforator surgery – procedure of choice
 - ii. Superficial venous ablation
 - iii. Endovenous laser ablation
 - iv. Valvuloplasty
 - b. Wound debridement – VLU are notorious for polymicrobial infection (suspected biofilm infection); routine weekly debridement is recommended to disrupt and help prevent biofilm infection²³¹
 - c. Tissue biopsy – ulcers present for longer than 3 months or which fail to respond to treatment after 4–6 weeks should be biopsied to evaluate for malignancy or other atypical causes of leg ulcers such as vasculitis, or cutaneous manifestations of systemic disease
 - d. Free tissue transfer – can provide durable treatment for large recalcitrant ulcers by improving venous hemodynamics and removing all lipodermatosclerosis-affected tissues that prevent ulcer healing.^{232,233}

Outcomes/prognosis/complications

1. Contact dermatitis – because of multiple prolonged exposures to topical agents
2. Soft tissue necrosis – when compression is applied to patients with concomitant arterial insufficiency
3. Malignancy – squamous cell and basal cell carcinomas are most common
4. Infection* – frequently polymicrobial, routine use of topical antimicrobial dressings is not recommended without a diagnosed wound infection
5. Deep venous thrombosis – stasis and inflammation are major contributing factors
6. Ulcer recurrence – approximately 50% of VLU recur within 10 years²³⁰

*Hints and tips – Hydrofera Blue® (Hollister, Inc.) is a foam dressing with gentian violet as the active antimicrobial agent. The foam dressing is absorbent, can be left in place under the compression wrap and gentian violet has broad antifungal and antibacterial activity (including MRSA and *Pseudomonas* spp.)²³⁴

Wound healing occurs as a well-coordinated series of biologic events. Clinical manifestations of dysregulated wound healing include: hypertrophic scars, keloids, and prominent granulation tissue, as examples of exuberant healing, while chronic wounds are stalled in the inflammatory phase. Every time a surgeon takes a scalpel to skin a wound is created. Understanding the fundamentals of wound healing will enable the surgeon to optimize conditions for good surgical outcomes. First and foremost attention should be paid to preparing the patient and the wound bed for healing or surgical coverage/closure.

Wound bed preparation

Patients with chronic open wounds typically have multiple comorbidities and these need to be medically optimized to ensure patients have the capacity to heal their wounds. Smoking cessation, adequate protein nutrition, and good glucose control as determined by hemoglobin A1c levels are essential. Patients with autoimmune or other inflammatory conditions need to have these controlled as well. For patients on chronic steroid therapy perioperative vitamin A



Fig. 13.20 Diabetic foot ulcer with multiple associated foot deformities including arch collapse, prominent metatarsal heads and claw deformity/hyperextension of toes.

Table 13.1 Medical comorbidities that impair wound healing

Malnutrition
Smoking
Renal failure
Radiation
Diabetes – poorly controlled
Heart failure
Hemoglobinopathies
Immunosuppression
Autoimmune inflammatory conditions – poorly controlled

supplementation may be beneficial to support wound epithelialization (Table 13.1).²³⁵

The physical examination of any wound, whether acute or chronic, must include palpation. Wounds should be probed for underlying fractures, retained foreign bodies, exposed hardware, communication with other joint spaces or body cavities and the presence of heterotopic bone when examining pressure ulcers. The presence of tunnels or undermining should be documented in the medical record. The periwound skin should be examined, looking for signs of additional injury such as induration, violaceous discoloration, redness, swelling, and signs of maceration including moist red skin with superficial ulceration (Fig. 13.22) and white rolled borders of the wound edge, called epibole (Fig. 13.23). One should look for the cardinal signs of infection (rubor, dolor, calor, tumor); and for chronic wounds pain has also been recognized as an indicator of potential underlying infection.^{236,237} However,



Fig. 13.21 Placement of absorbable antibiotic impregnated beads over debrided bone with known osteomyelitis



Fig. 13.22 Moisture-associated skin damage



Fig. 13.23 Epibole.

unless it is grossly apparent that the wound is infected, i.e., foul odor, purulent drainage with or without systemic manifestations of illness, then diagnosis of wound infection on the basis of clinical exam alone is unreliable.²³⁸ Biofilm infection of a wound suppresses the host inflammatory response, so physical signs of infection are not present. All of this information needs to be taken into consideration when performing debridement as part of the wound bed preparation.

Adequate debridement of wounds includes removal of all necrotic tissue and removal of epibole and periwound fibrotic tissue as these hyperproliferative cells do not migrate across the wound surface to promote closure.²³⁹ Unroofing areas of tunneling and undermining, specifically removing skin covering these areas even if the skin is healthy, needs to be done to provide adequate care of the wounds and facilitate planning of surgical coverage. Wound tissue biopsies for culture should be obtained once debridement is complete to determine whether bacteria remain in the wound. Sending the excised necrotic tissue for culture is not informative. Alternatives to sharp debridement include enzymatic debridement agents such as collagenase, mechanical debridement using wet to dry dressings, biodebridement using maggots, and non-contact low frequency ultrasound therapy (MIST® – Alliqua Biomedical).

Ensuring adequate wound bed perfusion and oxygenation is an absolute requirement for wound healing to occur. Oxygen is required for respiratory burst to kill bacteria, it is required for ATP production, cellular energetics, intracellular signaling and collagen synthesis. Elective debridement of wounds should not be performed until it has been established that there is adequate perfusion to support wound healing. For lower extremity wounds palpation of pedal pulses should always be the starting point. If pedal pulses are diminished non-invasive vascular studies such as ankle-brachial index, toe-brachial index, transcutaneous oxygen measurements, or imaging modalities that demonstrate blood flow such as laser speckle, or laser Doppler flowmetry can be used. For those patients who cannot be revascularized, have multiple comorbidities, and are immobile with no functional goals, dry stable eschar on the heels can be left intact.²⁴⁰ The term dry stable eschar denotes black eschar tightly adherent to the wound with no drainage, redness, or odor. These are essentially treated like dry gangrene that is allowed to auto-amputate as the wound bed below heals. The eschar should be debrided if signs of infection develop. Perfusion to wounds should be considered on an angiosomal basis, i.e., is the perforator vessel to the skin patent and is the source vessel for the perforator patent. If perfusion and oxygenation are poor due to source vessel obstruction or occlusion, then options for improving perfusion include peripheral vascular bypass or endovascular stenting. While permanent patency of stents is ideal, the objective is to have patency long enough to get wounds healed and eliminate the risk for limb loss. Reducing peripheral edema is also an important adjunct to improve tissue oxygenation as diffusion distance of molecular oxygen from capillaries is significantly decreased with tissue edema.

If pressure is a contributing etiologic factor then offloading measures need to be included to enable wound healing. For diabetic foot ulcers this would include modified footwear, total contact casting or non-weight bearing on the affected limb. For pressure injuries this would include the use of cushions to pad wheelchairs and protective boots to offload heels for patients who are bed bound.

Wound dressings

The selection of a wound dressing needs to be individualized to each patient. The ideal dressing according to the British National Health System is one that can absorb and contain exudate, does not leave particulate contaminants in the wound, provides thermal insulation, does not traumatize the wound bed when removed, is impermeable to water and bacteria, minimizes the frequency of dressing changes, and provides pain relief and comfort when used.²⁴¹ In general, inexpensive basic options for wound dressing should be tried first. If wounds fail to respond after wound bed preparation and use of first line therapies, then practitioners should progress to using advanced therapies. It should be noted that the Cochrane Database of Systematic Reviews has performed many meta-analyses on wound healing and states that there is no evidence to indicate the superiority of any type of wound dressing.^{241–243} A list of the different types of first line dressings and the indication for their use is included in Table 13.2.

Advanced therapies in wound healing

Growth factors

These are soluble factors that stimulate cells such as fibroblasts and keratinocytes via transmembrane glycoprotein receptors.²⁴⁴ Platelet-derived growth factor (PDGF) is most studied among the growth factors and a recombinant version (rhPDGF) showed positive effects in a randomized double blind study of DFUs.²⁴⁵ rhPDGF marketed as Regranex® (also called becaplermin) is the only FDA-approved growth factor product in the market specified for use in DFU treatment. This therapy has been shown to rely on ROS for biological functionality.²⁴⁶ It has also been shown to accelerate wound healing in irradiated wounds and abdominal wall separations.^{247,248} Another growth factor based product that is considered to be closer to the natural healing process is the autologous platelet gel (APG) treatment that is a composite of multiple growth factors derived from the patient's own blood. APG has been tested with chronic skin and soft tissue ulcers, burns, trauma surgery, etc., and has shown promise.^{249,250}

Extracellular matrix (ECM)

Acellular, collagen rich scaffolds derived from varied sources such as human or porcine dermis and porcine small intestinal submucosa (SIS) have been used for various procedures such as facial reconstruction and abdominal wall repair. AlloDerm® (human dermis), OASIS® (SIS) and MatriStem® (porcine bladder submucosa) have all been applied as treatments for different types of non-healing wounds (DFUs, VLU and PUs) and found to accelerate the process of wound healing.^{251–256} These ECM products are advantageous because they provide a scaffold containing collagen and additional growth factors such as TGF-β, VEGF and FGF, which combine to promote granulation and epithelialization of dermal wounds resulting in healing. There are also ECM products that do not contain bioactive growth factors, such as Prisma®, made of oxidized cellulose and collagen that has been shown to improve healing rates in diabetic foot ulcers in a small randomized controlled

Table 13.2 Common wound dressings

Dressing	Indications	Examples
Foam – hydrophilic polyurethane fibers absorb fluid	Light to medium exudate, comfort, protect against shear	Mepilex® (Mölnlycke)
Antibacterial – all the types of dressings listed here have antibacterial properties	Infected wounds	Manuka honey, silver, iodine, gentian violet, chlorhexidine, polyhexamethylene biguanide (PHMB), antibiotic ointments
Alginate – made from calcium alginate derived from seaweed, can absorb up to 20 times its weight in fluid	Highly exudative wounds – requires secondary dressing	Calcium alginate
Hydrogel – cross-linked gelatin or other insoluble fibers in solution with high water content	Hydration of desiccated wound bed to promote healing – requires secondary dressing	Duoderm® gel (Convatec)
Hydrocolloid – gelatin, pectin or carboxymethylcellulose bonded to stiff backing that is impermeable to water and bacteria	Superficial wound with minimal exudate and no tunnels or undermining, promotes autolytic debridement	Duoderm® (Convatec)
Hydrofiber – soft absorbent material that turns into a gel on contact with wound	Use to manage low to moderate exudate	Aquacel® (Convatec)
Charcoal infused	Odor management	Fungating tumors, foul-smelling wounds
Barrier creams	Protect periwound skin from maceration or fecal/urine contamination	Zinc oxide, Aloe Vesta® protective ointment (Convatec)
Protease modulating matrix – collagen substrate for the proteolytic enzymes present in wounds to protect wound bed from enzymatic degradation	Chronic wounds, moderate exudate	Promogran™, Promogran Prisma® (Acelity), Puracol® (Medline), Endoform™ (Hollister)

trial.²⁵⁷ Patients that responded well to the Prisma® product had decreased levels of MMP-9 and elastase at the wound site suggesting that the dressing may provide a substrate for enzymatic digestion to prevent soft tissue at the wound site from being targeted and limiting inflammation.

Engineered skin

Since the 1980s, the use of engineered biologic material for chronic wound therapy has evolved to expedite wound healing by providing scaffolds and release of growth factors to support cellular growth and re-epithelialization. Epidermal autografts were the first to show promise but had drawbacks related to the lack of a dermal component that have limited their applications. Apligraf®, a bilayered skin equivalent derived from neonatal foreskin and grown on bovine collagen matrix, showed promise in phase III clinical trials for chronic wounds such as venous ulcer and DFU and is now FDA approved for therapeutic use in the context of these ulcers.^{258,259} However, the allogeneic origin of the cells, growth on bovine collagen and lack of dermal structures such as hair follicles and sweat glands add a cautionary note on wide applicability. Dermalgraft® is a cryopreserved, three-dimensional human dermal substitute composed of human fibroblasts in a dissolvable mesh with an FDA approval for use in DFUs.²⁶⁰ It has also shown promise in other applications such as VLU and PU.²⁶⁰ Integra™ is a partial biologic dressing composed of a bovine collagen matrix and a glycosaminoglycan from shark cartilage associated with a temporary silicone epidermal sheet.^{260,261} This is indicated for use in partial or full thickness burn wounds and non-burn wounds such as VLUs, PUs and traumatic soft tissue reconstruction over exposed joints and bone.^{262,263}

Oxygen therapy

Hypoxia is a double-edged sword in wound healing and exists in wounds as a gradient from the center (most hypoxic) to the periphery (least hypoxic). While hypoxia plays a role in initiation of neovascularization upon acute exposure, chronic hypoxia is known to impair angiogenesis.^{264,265} Therefore the application of oxygen therapy to promote wound healing has value and indeed applied systemic hyperoxia (hyperbaric oxygen therapy (HBOT)) has been shown to effectively treat necrotizing infections, and increase angiogenesis, granulation tissue formation, wound contraction and secondary closure. There are currently 15 CMS-approved indications for HBOT treatment (www.cms.gov). This involves enclosing the patient in a special chamber where 100% oxygen at 2–3 atmospheres of pressure is applied for 60–120 minutes. The treatment is given 5 days a week for about 10–60 treatments depending upon the type of wound being treated. This results in saturation of oxygen-carrying capacity of hemoglobin and high levels of dissolved oxygen carried in the plasma. Dissolved oxygen in the plasma diffuses across the capillary bed in response to tissue oxygen gradients. This is a highly specialized treatment modality delivered by physicians and staff that have had additional training in hyperbaric medicine and administration of HBO therapy. There are some risks associated with this treatment including middle ear barotrauma with perforation of the tympanic membrane, seizures, hypoglycemia, and exacerbation of heart failure. However, the benefits of HBO are significant. A meta-analysis on HBO therapy for diabetic foot ulcers found that for every 4 patients that received HBO it prevented 1 major, i.e., below knee or higher level, amputation.²²⁴

Topical oxygen (TO) therapy involves the local application of 100% O₂ at slightly above 1 atmosphere pressure for 90 minutes once a day for 4 consecutive days followed by 3 days of no treatment. It has been shown to oxygenate superficial wound tissue up to 2 mm deep²⁶⁶ in the optimal therapeutic range (40–80 mmHg) that enhanced VEGF expression (unlike HBOT)²⁶⁷ and angiogenesis in human wounds. This treatment is typically given to patients in their home. Guidelines for the selection of patients and application of TO therapy for optimal use have been defined and suggest that this therapy could be considered for treatment of refractory wounds.²⁶⁸

Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is a well-known treatment modality used to promote healing in acute or chronic wounds. The basic concept of NPWT involves the use of a moistened foam or antimicrobial gauze dressing, covered with a transparent adhesive cover, attached to a vacuum pump that creates a sub-atmospheric pressure environment to the wound area. The intrinsic mechanotransductive properties of the skin are modulated for beneficial effects with the use of this therapeutic modality.²⁶⁹ The extrinsic tensile forces being applied to the wound surfaces are proposed to (a) cause shrinkage of wound area because of mechanical contraction, (b) apply a microstrain that alters the shape and function of individual cells, (c) remove fluids and reduce edema thereby inducing a return to osmotic homeostasis and (d) maintain a moist and stable wound environment which is conducive to healing.^{269,270} This therapy can be adapted to meet individual patient needs in combination with other therapies (antimicrobial silver, skin substitutes such as Apligraf® and Integra™ and a wireless electroceutical dressing)^{270–273} and has been indicated to be useful in the case of DFU and VLU.^{274,275} However, a serious complication associated with this treatment is bleeding and therefore it should not be placed directly over areas of vascular repair or anastomosis.²⁷⁶

Electroceuticals

An intrinsic electric field and natural direct currents are present in the skin and are essential for normal regeneration in lower vertebrates, and their reversal induces degeneration. The human skin maintains an intrinsic transepithelial potential (TEP) in the intact skin. When the skin is wounded, the potential difference between the wound and the surrounding intact skin generates an endogenous electric field (10–100 μA/cm²) around and directed into the site of the wound and the cells within this field respond to the presence of this field.^{277–282} Electrostimulation (ES) therapy is based on the premise that

an externally applied electric field can then result in an electric current being driven along the wound surface, enhancing the endogenous electric field and aiding the healing processes. This field has been shown to promote several major signaling cascades that influence the directed migration of numerous cells (such as keratinocytes, fibroblasts, endothelial cells and immune cells) that are integral to the wound healing response.²⁸³ Although the concept of ES therapy has existed for over a hundred years, it has primarily impacted neuronal stimulation (cochlear implants, spinal cord, deep brain stimulation) and cardiac function (pacemakers) and there are FDA approvals for many of these applications.^{284,285} The use of ES for wound care applications has been slowly gaining momentum. Several clinical trials have addressed the application of various types of electrical stimulation such as direct current (DC), alternating current (AC), high-voltage pulsed current (HVPC) and low-intensity direct current (LIDC) for all types of chronic wounds.^{285,286} However, some limitations include ease of application of these treatments and variations in efficacy of the different ES treatments because of lack of standardized parameters (voltage, type of current (direct vs alternating), mode and length of time for treatment) for use. In 2002, Centers for Medicaid/Medicare Services approved reimbursement of ES treatments of chronic ulcers that did not respond to standard therapies.²⁸⁷ The FDA has not yet approved ES applications for wound care with the exception of a woven bandage with embedded microbatteries that acts as a wireless electroceutical dressing (WED).²⁸⁸ Microcell batteries of silver and zinc, activated by a moist environment, generate an electric field of 0.1–1 V which stimulate wound healing and provide antimicrobial protection (Procellera™, Vomar Innovations). The molecular mechanisms involved in the enhancement of wound healing by ES have been studied *in vitro*. Electric fields generated by this dressing improved keratinocyte migration via redox-dependent processes²⁸⁹ and disrupted bacterial biofilm by repressing quorum sensing and redox-sensitive multidrug efflux pathways.²⁹⁰ This novel electroceutical dressing, used in conjunction with NPWT in a randomized clinical trial, decreased the frequency of dressing change and lowered the cost of the associated wound care.²⁷³

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Scar prevention, treatment, and revision

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SYNOPSIS

- Preventing and treating problem scars are vital to patient satisfaction and good outcomes in all surgical cases, ranging from the most precise aesthetic work to the most challenging reconstructive procedures. Understanding how scarring occurs helps to structure our surgical planning, approach, and technique. In follow-up care, minimizing scarring can lead to improved form and function as well as increased patient satisfaction. Even long after recovery, patients with pathologic or abnormal scarring may seek the expertise of a plastic surgeon for scar revision. However, even the most experienced surgeons can attest to the challenges of managing scar tissue in reoperative surgery.
- To begin to tackle such obstacles, plastic surgeons have created an arsenal of tools based on the central tenets of our discipline. Published in 1957 by Gillies and Millard, *The Principles and Art of Plastic Surgery* set out fundamental doctrines of plastic surgery and defined the foundational knowledge of our field.¹ Operative scar treatment and revision procedures rely heavily on these principles. Ideas such as diagnosing before treating, making a plan, marking landmarks, “borrowing” tissue from other areas, and restoring the beautiful normal represent our approach to the management of scars. Instead of having a specific operation for each defect, the plastic surgeon is charged with using these principles to optimize therapeutic options for each individual patient.
- To the surgical armamentarium we continue to add our growing understanding of scar biology. Fetal models have shed light on the complex factors that determine scarring versus scarless wound healing. In addition, we have deepened our understanding of the mechanisms that lead to pathological hypertrophic and keloid scar formation. Such advances in cell and tissue biology have revealed many new therapeutic targets, which are currently under active investigation.
- Each treatment plan begins with the patient. A good treatment outcome is rarely achieved without first understanding the patient’s antecedent experience, current complaints, and future expectations. Here we will describe important aspects in approaching a scarred patient, assessing a scar and understanding scar biology. We will then focus on strategies for preventing, treating, and revising scars. These

strategies are defined by both modern advancements in medicine as well as time-proven principles of surgery.

Personal and social significance of scars

For physicians, scars represent an endpoint in wound healing. For patients, however, scars exemplify something far more deeply personal and emotional. Scars caused by disease, violent trauma, or aberrations of development can result in lifelong physical and psychological burdens. Treating scars thus requires an understanding of the psychological and social distress a patient may experience.

Scars may arise from both culturally sanctioned and prohibited practices. Ritual scarring, or cicatrization, was an important part of identifying tribal belonging in parts of Africa and Australia.² In tribal communities in Sudan and Papua New Guinea, the prevalence of keloid formation in certain racial groups was exploited for spiritual and cultural markings. Likewise, the Japanese art of tattoo, or *irezumi*, carried sufficient cultural weight as to be banned by the Meiji government until 1945, when occupational forces again legalized its practice. Today tattooing and, to a lesser degree, branding and scarification, continue to be a popular form of self-expression.³

Gender plays a clear role in the effect of scars in society. A recent study suggested that facial scars in men indicate risk-taking and bravery, and these men are subsequently perceived as more attractive.⁴ The same effect was not found when observers were shown similarly scarred women. Nevertheless, many scars carry negative social implications for both genders. Studies of quality of life measures in burn patients reveal that scars cause significant decrease in the quality of patients’ social and professional life.⁵ For instance, both depression and post-traumatic stress disorder (PTSD) have been identified as potential long-term sequelae, with rates for PTSD in burn patients ranging from 23% to 45% at 1 year

following injury.⁶ Risk factors include avoidant coping strategies and pre-existing psychiatric history, as well as hand and face involvement and burn severity.⁷ Therefore understanding the specific aspects of the patient's life most affected by the presence of scarring can help direct both medical and non-medical therapy.

Psychologist Thomas F. Cash described the importance in reconciling a patient's "view from the outside" and "view from the inside" when coping with deformity.⁸ Understanding the social context and patient's emotional relationship to scars is vital to treatment. A potentially useful tool in understanding and assessing these variables is *Psychological Aspects of Reconstructive and Cosmetic Plastic Surgery: Clinical, Empirical, and Ethical Perspectives*.⁹ This title reflects a multidisciplinary effort of leading psychologists, psychiatrists, and surgeons in determining and delivering care to patients with real or perceived deformities.

History and physical examination

As with the evaluation of most maladies, assessment of a patient with an unsatisfactory scar begins with a focused history and targeted physical examination (Box 14.1). While obtaining the history, the etiology of the scar and relevant associated factors (e.g. prior dissatisfactory surgery, relation to violent crime or infection) should be elucidated. In communicating with the patient, the treating physician should be empathetic without attempting to attribute the patient's current complaints to care provided by prior treating physicians. This can usually be accomplished by focusing on the problem at hand and appropriate next steps.

The physical exam includes an assessment of both the scar and surrounding tissue. With facial scars, attention must be paid to normal folds and features as determined by the aesthetic subunits.¹⁰ Examination of other scars on the patient to determine predisposition to poor scarring can also be helpful. Evaluation of the scar should include written and photographic documentation of size, color, and texture. The relationship of the scar to surrounding structures in motion and repose should be carefully assessed to determine tethering and contracture.

Scar formation can cause functional, aesthetic, and emotional problems. Before initiating treatment, the physician

BOX 14.1 Key points

History

Etiology

History of infection

Associated symptoms (pain, itching)

Radiation and steroid exposure

Physical exam

Size, color, texture

Relationship to normal structures

Tethering and contracture

Changes with movement

Table 14.1 The Vancouver Scar Scale

Pigmentation	
0	Normal: color that closely resembles the color of the rest of the body
1	Hypopigmentation
2	Hyperpigmentation
Vascularity	
0	Normal: color that closely resembles the color of the rest of the body
1	Pink
2	Red
3	Purple
Pliability	
0	Normal
1	Supple: flexible with minimal resistance
2	Yielding: giving way to pressure
3	Firm: inflexible, not easily moved, resistant to manual pressure
4	Banding: rope-like tissue that blanches with extension of the scar
5	Contracture: permanent shortening of the scar, producing deformity or distortion
Height	
0	Normal: flat
1	<2 mm
2	<5 mm
3	>5 mm
(Reproduced from Sullivan T, Smith J, Kermode J, et al. Rating the burn scar. <i>J Burn Care Rehabil.</i> 1990;11:256–260.)	

must take the time to understand and address each of these elements. The extent of scar should be considered along with the patient's goals in getting treatment. Arriving at realistic targets and expectations may require multiple visits or a combination of surgery and counseling. Frequently, scheduling a second or third visit to ensure the patient understands the treatment plan and has realistic expectations prior to undergoing the planned procedure is in the surgeon's best interest.

Assessing scars

Clinical evaluation of a scar is necessary in determining the best course of treatment and effectiveness of therapy. The ideal scale for scar assessment should demonstrate validity, inter-observer reliability, and clinical applicability. Though multiple objective and subjective assessment tools have been devised to characterize scars, there is as yet no universal consensus on scar grading. However, the most frequently used measure is the Burn Scar Index, also known as the Vancouver Scar Scale (VSS) (Table 14.1).¹¹ Originally published in 1990, the VSS is an observer-dependent scale designed to assess changes in burn scars with maturity and in response to

treatment. Scars are assessed based on four variables: pigmentation, vascularity, pliability, and height. Scores are then assigned across these four variables based on the degree of variance from normal skin. When applied, the scale can be a useful tool for prognosis and treatment evaluation. In 1995, Baryza and Baryza¹² found that adding a low-cost instrument could improve inter-observer reliability. They combined a ruler, a transparent piece of plastic, and a scoring “cheat sheet” to aid in measuring, blanching, and determining the score, respectively.

While perhaps the most commonly used assessment tool, the VSS is limited by its historical focus on burn scars, lack of consideration of patient’s own perceptions, exclusion of pain and pruritus, as well as a lesser applicability to larger scale heterogeneous scars.¹³ Other evaluation measures, such as the Visual Analog Scale (VAS), the Patient and Observer Scar Assessment Scale (POSAS), the Stony Brook Scar Evaluation Scale (SBSES), and the MCFONTZL classification system have been created with varying levels of validation and adoption.¹⁴ The large variety of different scales reflects the relative imperfection of each individual system.

The VAS assesses parameters such as color, contour, and texture to correlate intra-observer as well as photographic and histologic findings.¹⁵ The scale can be applied to both burn and surgical scars. Similarly, the POSAS was developed in 2004 for burns and has since been validated for linear scars. This scale has the benefit of incorporating patient opinion to a VSS-like scale and can better assess symptoms such as pain, itchiness, and thickness.^{16,17} A third scale, the SBSES, is a photo-based scale similar to VAS and was initially developed as a tool for emergency medicine physicians to evaluate wounds from 5 to 10 days after wounding up to the time of suture removal.¹⁸ The SBSES has since been adapted for long-term evaluation of scars 3 to 12 months after injury and has been used as an outcome measure in Food and Drug Administration-mandated clinical trials.¹⁹ Lastly, the MCFONTZL classification system was developed specifically for facial trauma (Table 14.2).²⁰ This system incorporates billing and uses a mnemonic to divide the face into the maxilla, chin, forehead, orbits, nose, temple, zygoma, and lip. These scales have been useful in comparing outcomes from conventional versus minimally invasive surgery, use of wound

closure adhesives, and new therapeutic agents for scar treatment.

A number of instruments have also been used to facilitate objective assessment of scars. Blood flow has been analyzed by laser Doppler, while depth and color have been studied by ultrasound and spectrometry.²¹ Skin elasticity meters, commercialized for evaluation of scleroderma, have also been used to examine scars.²² Lastly, three-dimensional systems have been used in a number of studies to create high definition and easily reproducible topographic representation of scars. While these instruments demonstrate a high degree of accuracy, reliability and clinical utility, the added expense and additional technical training required have limited them largely to research settings.

Scar biology

Scar formation is a physiologic response to injured tissue and reflects the body’s attempt to restore tissue strength and integrity. The imperfect nature of this process likely reflects a trade-off of organization for debridement and sterilization, and results in distinct morphologic differences between scarred and normal tissue. A mature scar, the final product of normal wound healing, is characterized by a disorganized array of collagen and loss of dermal appendages. However, scars are not static entities. Instead, scar formation is a dynamic process, beginning at the initial injury and proceeding temporally through the phases of wound healing to produce a mature scar (Fig. 14.1).

Normal wound healing is a complex process that can be roughly divided into three overlapping stages: inflammation, proliferative matrix formation, and remodeling. Inflammation, the first stage of wound repair, is characterized by infiltration of immune cells attracted by various cytokines, invading pathogens and growth factors towards the wound site. Platelets also aggregate at the site of injury, resulting in activation of the coagulation cascade and leading to the formation of a fibrin clot.²³ This initial cellular response is aimed at the establishment phagocytosis of injured cells and hemostasis. In a non-infected wound, inflammatory cells are then replaced by fibroblasts in the proliferative stage of wound healing. This phase is characterized by synthesis and secretion of the extracellular matrix (ECM).

ECM is formed through a highly regulated process of synthesis, deposition, and degradation by fibroblasts that migrate to the wound in response to TGF- β , PDGF and other growth factors. The initial wound environment is largely composed of fibrin and the glycosaminoglycan hyaluronic acid. As fibroblasts populate the wound, enzymes degrade the matrix and collagen is deposited. Cross-linking and organization of the collagen ultimately create tensile strength across the wound. The process of collagen deposition and degradation is in part determined by the regulation of matrix metalloproteinases (MMPs), which in turn, are inactivated by proteins called tissue inhibitors of metalloproteinases (TIMPs). The balance of MMP-TIMP function remains an active area of research in wound healing and scar biology.²⁴

At the cellular level, scars are characterized by a lack of connective tissue organization compared to surrounding normal tissue architecture. Grossly, the early or immature scar is red because of its dense capillary network. Over a period

Table 14.2 MCFONTZL assessment system

A area	MCFONTZL aesthetic unit designation
S Side	
T Thickness	Depth of penetration
E Extension	Branching
R Relaxed skin tension line conformity	Directionality (relaxed skin tension lines)
I Index laceration	Laceration with maximum continuous skin interruption
S Soft-tissue defect	
K Coding	Current procedural terminology code
(Reproduced from Lee RH, Gamble WB, Robertson B, et al. The MCFONTZL classification system for soft-tissue injuries to the face. <i>Plast Reconstr Surg</i> . 1999;103:1150–1157.)	

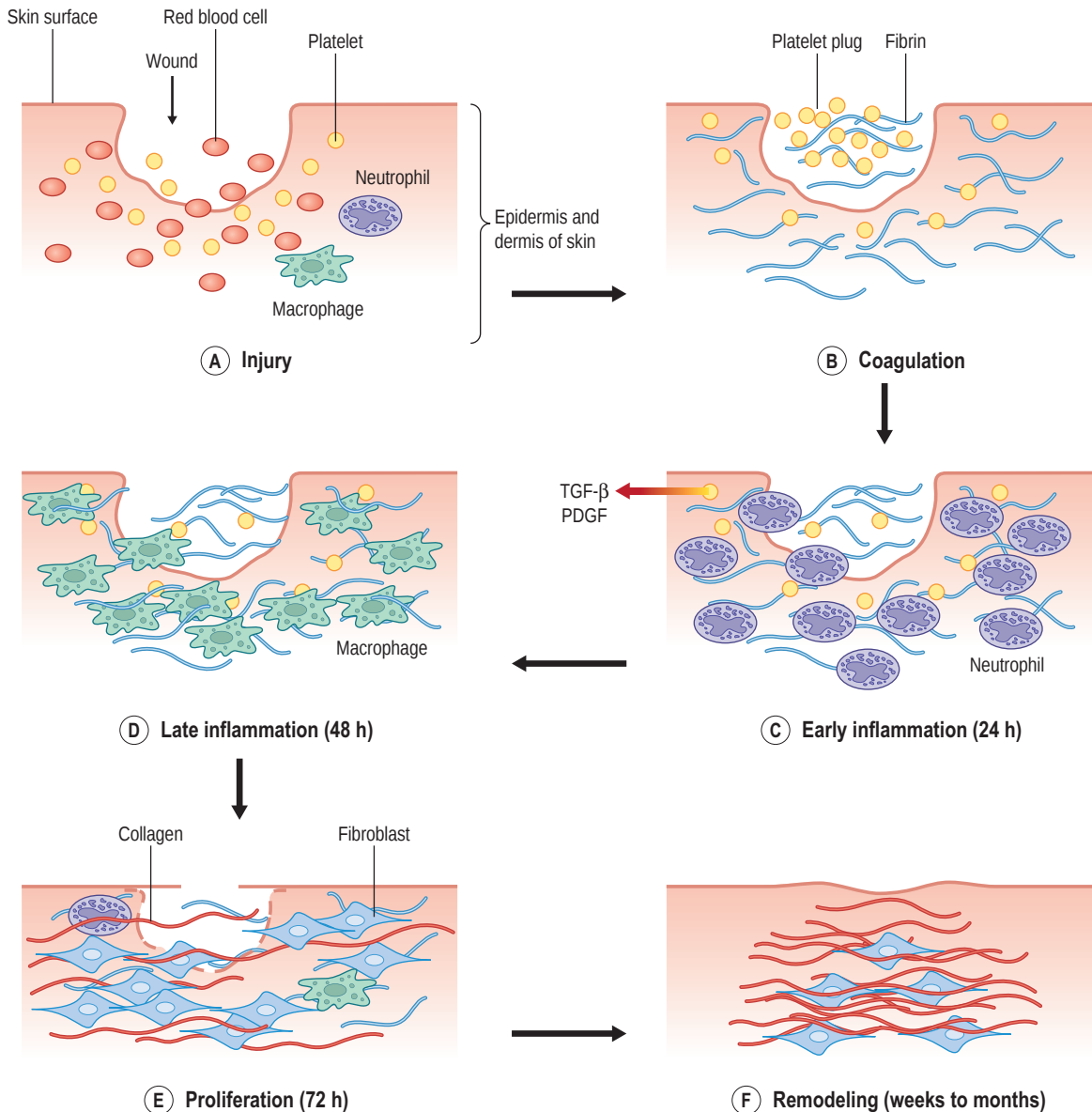


Fig. 14.1 (A–F) Phases of wound healing. Wounds progress through inflammation, proliferation, and finally remodeling. TGF- β , transforming growth factor- β ; PDGF, platelet-derived growth factor.

of months, the capillaries regress until relatively few remain and the red color fades. The scar remodels slowly over months to years to form a “mature” scar. Mature scars are usually hypopigmented and appear lighter than the surrounding skin. However, they can occasionally be hyperpigmented and darker than the surrounding skin. Hyperpigmentation is more common in darkly pigmented patients or lighter-pigmented patients whose scars receive excess sun exposure. For this reason, surgeons recommend sun protection for patients with early scars on sun-exposed areas such as the scalp, face, and neck.

During the remodeling phase, wounds gradually become stronger with time. Wound tensile strength increases rapidly from 1 to 8 weeks following initial injury. Thereafter, tensile strength continues to increase, albeit at a slower pace, and has been documented to continue to increase up to 1 year in

animal studies (Fig. 14.2). Nevertheless, the tensile strength of wounded skin only reaches approximately 80% of the tensile strength of unwounded skin at best. A mature scar, the final result of tissue repair, is brittle, inelastic, and without skin appendages such as hair follicles or sweat glands. The cost of these imperfections is counterbalanced by the benefits of rapid re-establishment of tissue integrity, debridement, and sterilization of contaminated wounds.

Conditions of excessive scarring

Wound healing is a tightly regulated process involving cell–cell signaling and environmental cues. In normal wounds, repair slows when the dermal defect is closed and epithelialization is complete. But when appropriate signals are absent

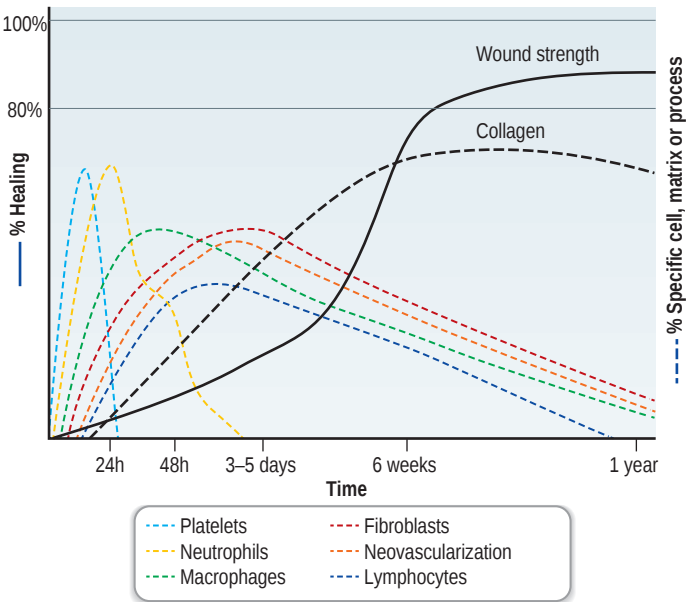


Fig. 14.2 Wound tensile strength with time. Wounds reach approximately 80% of their preinjury tensile strength at 6 weeks. Further gains occur slowly over time and never achieve 100% preinjury strength.

or ineffective, the repair process may continue unabated and result in surplus scarring. Hypertrophic scars and keloids, both fibroproliferative disorders of wound repair, are two examples of this.

In general, both keloid and hypertrophic scar fibroblasts have an upregulation of collagen synthesis, deposition, and accumulation. However, the underlying regulatory mechanisms responsible for this excessive repair are still under investigation. Both profibrotic cytokines such as transforming growth factor- β 1 (TGF- β 1) as well as a lack of programmed cell death, or apoptosis, of activated fibroblasts secreting ECM components have been implicated in excessive scarring.^{25,26} For unknown reasons, hypertrophic scars and keloids are unique to humans and do not naturally occur in other animals.

Normotrophic, hypertrophic, and keloid scars vary little histologically.²⁷ Pathological scar types are therefore distinguished based on clinical characteristics. Hypertrophic scars continue to thicken and rise instead of flattening and shrinking like mature scars, but stay within the original scar boundary. In contrast, keloid scars grow beyond the boundaries of the initial wound (Table 14.3). Because the timeline from immature to mature to hypertrophic and keloid scar formation can vary due to a number of factors, diagnosis is not always clear. Clinical monitoring of scar evolution with frequent serial examinations is the most important strategy for diagnosing

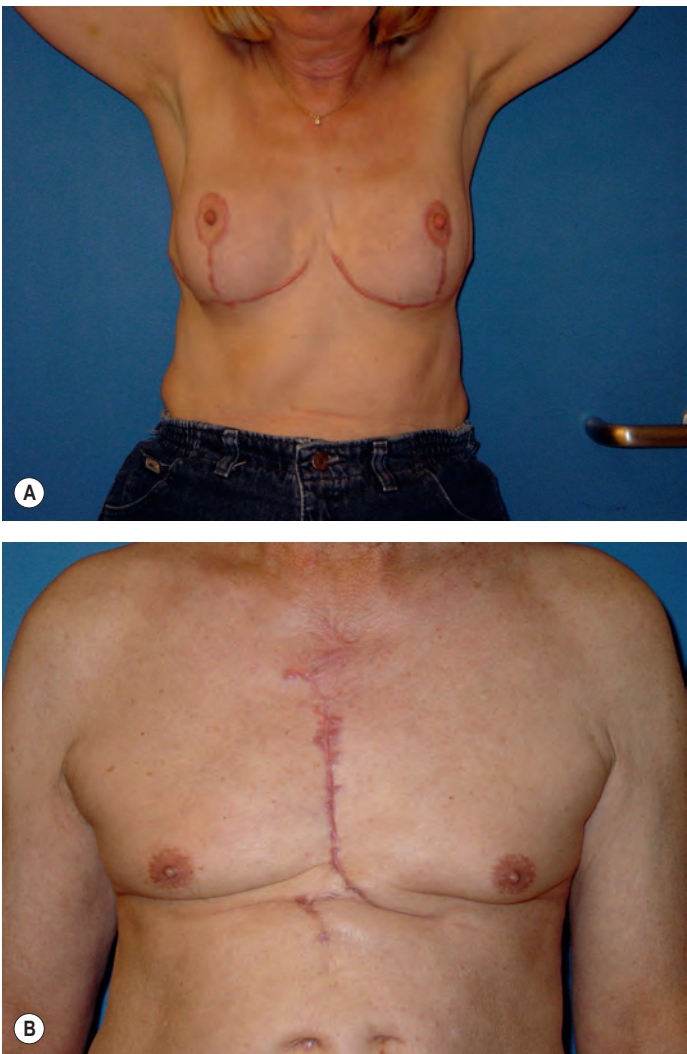


Fig. 14.3 (A,B) Hypertrophic scars.

and treating the problem scar. Early application of treatment modalities, discussed in depth later in this chapter, can often prevent further progression and even reverse scar pathology.

Hypertrophic scar

Hypertrophic scars are defined as pathologic scars that have not overgrown the original wound boundaries, but are instead abnormally thickened and raised (Fig. 14.3). Hypertrophic scars are often painful and pruritic. This is thought to be due to release of proinflammatory neuropeptide substance P from nerve endings following injury.²⁸ Hypertrophic scars usually

Table 14.3 Types of scar			
	Appearance	Growth pattern	Cause
Normal mature scar	Hypo- or hyperpigmented, flat	Contracts slowly over time	Normal tissue repair
Immature scar	Red, slightly elevated, sometimes itchy	Turns into mature scar	Normal tissue repair
Hypertrophic	Raised, itchy, painful, confined to its borders	Self-limited, but may take years	Excess mechanical stress
Keloid	Raised, itchy, extending into normal tissue	Continued growth; recurs	Genetic predisposition; can result from minor trauma

form secondary to excessive tensile forces across the wound and are most common in wounds across flexion surfaces, the extremities, breasts, sternum, and neck.

Hypertrophic scarring is a self-limited process and usually regresses with time. These scars eventually fade in color and flatten to the surrounding skin level, though the unaided process may take years. No clear histological differences between hypertrophic scars and keloids exist. Early studies found that keloids contained bundles of collagen around focal nodules of proliferation.²⁹ Later studies, however, refuted this distinction.

To date, clinical treatment of hypertrophic scars remains unsatisfactory, and is reflective of our incomplete understanding of mechanisms underlying hypertrophic scar formation. The creation of consistent and reproducible models for testing new treatment modalities, particularly animal models of hypertrophic scars, is key to advancing our knowledge of hypertrophic scar biology.^{30,31}

Keloid

Scars that overgrow the original wound edges are called keloids (Fig. 14.4). This clinical characteristic distinguishes

keloids from hypertrophic scars. True keloid scars are not common and occur predominantly in darkly pigmented individuals, with an incidence of 6–16% in African populations. This demonstrates genetic predisposition with autosomal-dominant features. The keloid scar behaves like a benign skin tumor with continued slow growth, and in the majority of cases complete excision with primary closure of the defect results in recurrence.

Keloids consist primarily of collagen. They are relatively acellular in their central portions with fibroblasts present along their enlarging borders. Keloids do not, however, contain a significantly elevated number of fibroblasts. Rather it appears that collagen deposition outpaces degradation, allowing the lesion to enlarge.

Keloid formation may be the result of excessive stimulation or an inappropriate response to stimulation. *In vitro* studies find that keloid keratinocytes and fibroblasts respond differently to growth factors found at the repair site. TGF- β treatment, for example, causes a greater degree of collagen gene expression in keloid compared to normal wound fibroblasts.³² In addition, a greater degree of profibrotic growth factor expression occurs in keloids compared to normal wounds.³³ Together, these and other studies suggest that keloid



Fig. 14.4 (A–D) Keloids. (With permission from Dr. Shelly Noland.)

formation occurs because of increased expression and activity of proliferative growth factors at the wound site.

Alternatively, a defect affecting the repair process may result in the absence of appropriate “stop” signals for healing. In this proposed mechanism, a lack of stop signals in the wound results in continued and unchecked repair. Studies of apoptotic cell numbers have found similar amounts of apoptotic cells at the advancing wound edge in both normal and hypertrophic scars. In keloid scars, however, decreased expression of apoptotic genes was found.³⁴ The biology of keloids continues to raise important questions about what factors govern normal and pathologic healing.

Prevention

Surgical technique

The molecular regulation of scar formation aside, meticulous surgical technique continues to be the cornerstone of successful scar minimization (Box 14.2). To begin, the plastic surgical craft utilizes fine instruments and atraumatic technique to minimize trauma to tissue. For example, hooks for retraction and avoidance of double grasping with forceps help prevent crush injury to delicate tissue.

Obtaining a fine pencil-line scar also relies on relieving tension on the apposed epidermal edges (Fig. 14.5). Undue tension clearly plays a role in widened and hypertrophic scars. Wound tension causes edge separation and scar widening with time. Wound edges that are sharply defined and aligned without tension heal with the least amount of scarring. This is accomplished by approximating tissue with deep buried subdermal stitches to minimize tension of overlying tissue before final apposition. Additionally, the Gillies near-far pulley can be used to aid approximation of higher tension tissue. Skin eversion can be seen as an exaggerated application of the principle of tension-free closure and can be accomplished with horizontal mattress and “flask-shaped” simple sutures. However, care must be taken not to strangulate tissue with overly tight stitches.

To prevent Burrow’s triangles (“dog ears”), sutures should be placed at the wound periphery so that redundancy can be worked towards the middle, allowing for cleaner alignment along the epidermis of the two wound edges during apposition. When tissues of differing thicknesses are closed, care should be taken to capture a deeper bite of the thinner tissue and a more superficial bite of the thicker tissue for proper alignment. Likewise, when tissues are at differing heights, taking a deeper bite of the lower tissue can help bring that tissue level.

BOX 14.2 Surgical technique

- Atraumatic technique
- Minimizing tension
- Skin eversion
- Perfect apposition
- Use of natural skin tension

Final closure can be achieved through fine interrupted and mattress stitches if care is taken for prompt suture removal. Removing sutures on the face should be performed no later than 3 to 5 days after placement. If necessary, the wound can be reinforced with adhesive tape strips at the time of suture removal. Failure to remove stitches in a timely fashion can result in a disfiguring railroad scar pattern from stitch marks.

Alternatively, subcuticular stitches or adhesive tissue glue can be used for final skin apposition. Permanent sutures such as polypropylene (e.g., Prolene®, Ethicon) or nylon incite less of an inflammatory reaction than absorbable biodegradable sutures. However, both permanent and absorbable subcuticular stitches can be left untied with the ends secured by tape to avoid granuloma formation around knots. Removal of permanent subcuticular suture can be aided by interval externalization of the stitch so the entire stitch does not have to be pulled through the wound.

To minimize visible scarring, elective incisions are least noticeable when placed parallel to the natural lines of skin tension (Langer’s lines) (Fig. 14.6). This placement location has two advantages: the scar is parallel or within a natural skin crease, which camouflages the scar, and the location places the least amount of tension on the wound.

Patient-specific factors

Factors that contribute to poor wound healing can also contribute to poor scarring. Poor nutrition, diabetes, obesity, and radiation exposure impair healing, and lead to an increased risk of infection. Patients with these comorbidities are at higher risk for wound complications and poor scarring. Medications such as corticosteroids and isotretinoin can also negatively affect tissue healing. Lastly, though the exact mechanism has yet to be determined, genetics plays a role in scarring, as demonstrated most dramatically in keloid formation.

Wound infections and foreign-body reactions

Wound infections and foreign-body reactions can lead to wound dehiscence and poor scarring. Increased proinflammatory cytokines may trigger abnormal fibroblast responses.³⁵ Leaving the initial dressing on for 48–72 hours, the time needed for epidermal closure, is a frequently used strategy to maintain wound sterility. Efforts to prevent wound infection, including debridement of any devitalized tissue and administration of perioperative antibiotics when indicated, should be a priority.

Adjunct therapy

As previously discussed, minimizing tension has been linked to decreased scarring.³⁶ Recently, a silicone elastomeric dressing that mechanically off-loads tension has been shown in two prospective, randomized controlled clinical trials to reduce scarring after scar revision surgery and abdominoplasty (Fig. 14.7).^{37,38} The device was applied 1–13 days following closure of an incision and applied weekly for 12–13 weeks. This tension off-loading device is a powerful new technology that represents the first and only level I evidence for scar reduction. Ongoing research may further demonstrate the effectiveness of this therapy for hypertrophic scars and keloids.

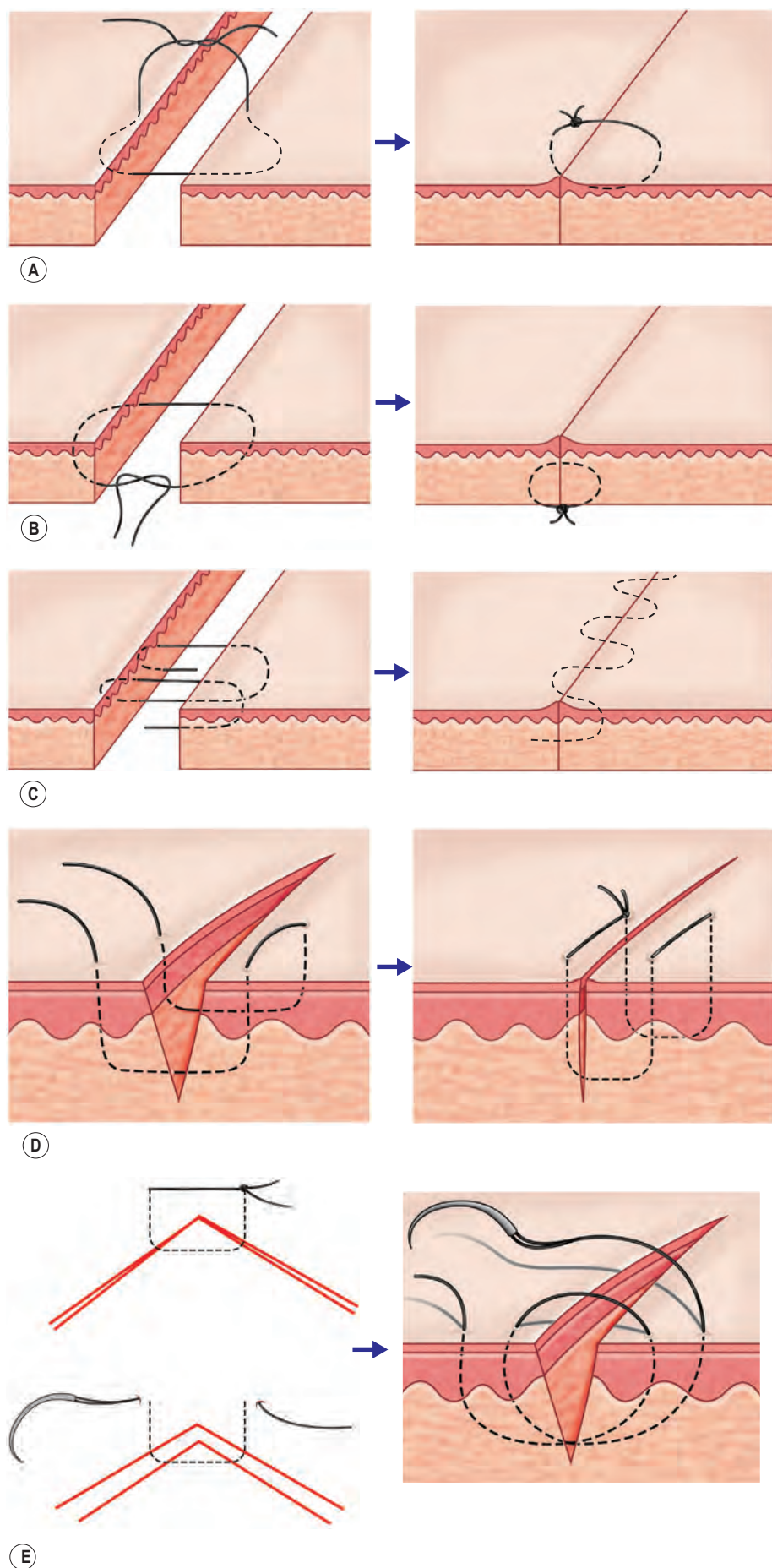


Fig. 14.5 (A–E) Skin eversion technique. Application of deep stitches approximates the dermis and relieves tension on the epidermis, contributing to less scar widening.

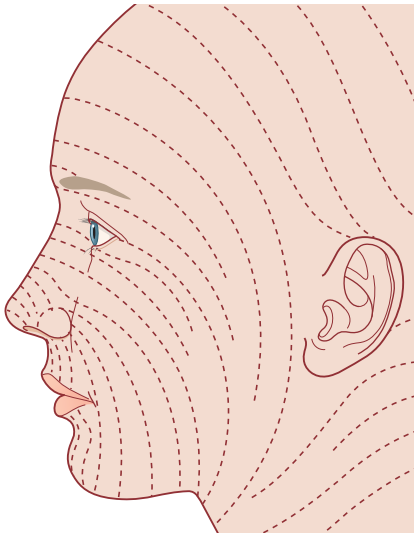


Fig. 14.6 Langer's lines.

Taping and coaptive films have also been used as adjunctive therapy to prevent abnormal scarring.^{39,40} Silicone gel sheeting, discussed in more detail later, has been considered first-line prophylaxis although evidence is weak. Treatment begins shortly after wound epithelialization, is worn 12–24 hours per day and continued for at least 1 month. Breast and abdominal binders work as external splints to decrease skin tension further. As with internal sutures, care should be taken not to constrict adequate blood flow to the wound edge. Current recommendations encourage the prophylactic use of these measures in patients who have wounds in high-risk areas such as the breast and thorax, or who have previously developed abnormal scarring.⁴¹

Studies of over-the-counter remedies such as vitamin E and onion extract have failed to provide good evidence in support of their use.^{42–44} These studies have been criticized, however, for their small sample size.⁴⁵ Modalities such as massage, hydrotherapy, and ultrasound also need additional investigation before their role in treatment of scars can be determined.

Lastly camouflage techniques can be a useful adjunct in addressing the psychosocial dimension of scar management. These strategies can be incorporated as a nurse-led aspect of a practice and may positively affect patient quality of life.^{46,47} A new spray-on, computer color-matched camouflage, Microskin, has been shown to improve psychosocial measures in pediatric burn patients.⁴⁸ The product is purported to be water- and sweat-proof, requiring reapplication every 4 to 5 days.

Treatment

Plastic surgeons today must apply surgical, nonsurgical, and multimodal strategies in treating disfiguring and pathologic scars. Treatment should be guided by diagnoses. Proper diagnosis requires addressing the patient's complaint, assessing the characteristics of the scar, and understanding the state of the scar with respect to scar biology. For instance, the approach to a 17-year-old male emotionally burdened by mature acne scars involving multiple facial subunits may require a combination of counseling and nonsurgical modalities. Alternatively, the functional impairment experienced by a 45-year-old woman with hypertrophic scar limiting elbow range of motion may require more invasive intervention. In general, noninvasive strategies as described below offer a good starting point in the treatment algorithm.

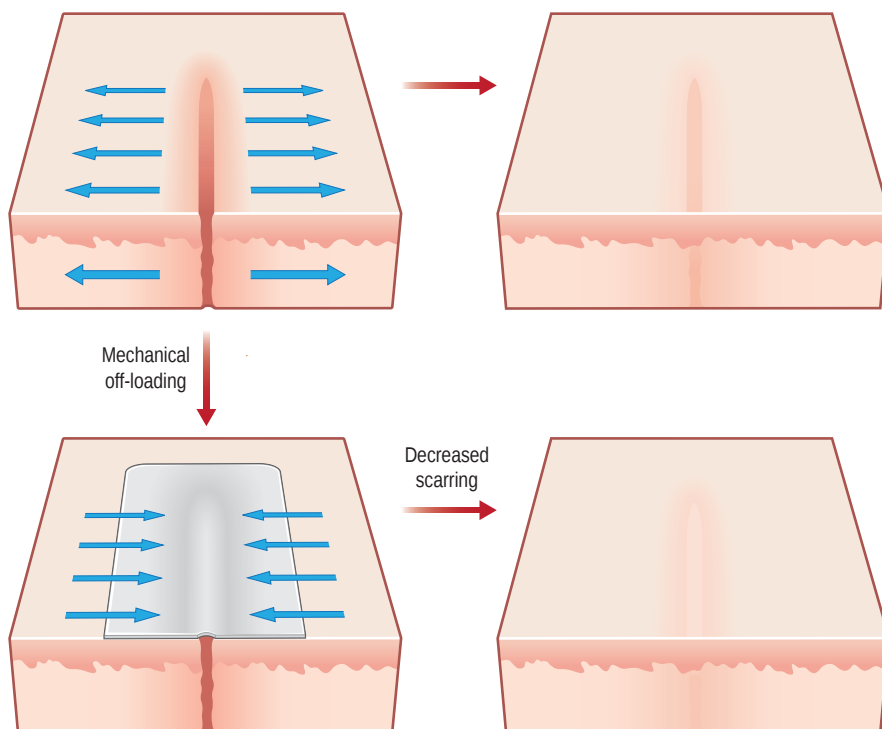


Fig. 14.7 Tension off-loading dressing.

Treatment of hypertrophic scar

Treatment options for hypertrophic scars include the application of pressure garments, silicone sheets, corticosteroids, laser therapy, and re-excision with primary closure. Primary closure is most useful in cases of excess scarring caused by infection or dehiscence. If the original wound was closed following the basic tenets described above, then re-excision with primary closure is not likely to result in an improved scar compared to the initial procedure. Recurrence of hypertrophic scarring is quite high in these circumstances. Most surgeons, therefore, do not treat hypertrophic scars with excision and primary closure unless adjuvant therapy is also planned.

Silicone gel sheeting can both prevent hypertrophic scar formation and accelerate its involution. Though a 2006 Cochrane review found only weak evidence to support silicone sheeting, multiple randomized control trials (RCTs) have since reconfirmed its value.⁴⁹ Silicone gel sheeting has demonstrated the ability to dramatically hasten hypertrophic scar maturation and decrease associated symptoms of pain, rigidity, and pruritus.^{50,51} However, silicone-containing oils and creams have also exhibited mixed efficacy and silicone's mechanism of action in treating hypertrophic scars is still under debate.⁵² One line of evidence points to increased hydration from occlusion with subsequent decrease in inflammatory cytokines.^{53,54} Alternative suggested mechanisms include a direct effect by silicone particles and an increase in static electrical fields.^{55,56} Studies of related polyurethane- and glycerin-based occlusive dressings are mixed, with some studies demonstrating effectiveness equal to silicone.^{57,58}

Since adoption in the 1970s, the use of compression garments has been a mainstay of burn scar management. Evidence in the literature, however, has been less clear-cut. A prospective RCT of 122 burn patients by Chang *et al.* failed to show significant improvement in time to scar maturation.⁵⁹ Conversely a subsequent, more precise RCT in 2005 by Van den Kerckhove *et al.* using both subjective and objective measures found improved scar thickness when garment pressure was above 15 mmHg.⁶⁰ Yet another study, a 2009 meta-analysis of six RCTs, including those mentioned above, found only marginal improvements of questionable clinical significance in scar thickness.⁶¹ To date various clinical studies are ongoing and the utility of compression garments in treating hypertrophic scars remain under debate.

Intralesional corticosteroid injections offer a second line of therapy for hypertrophic scars refractory to silicone gel sheeting. The exact mechanism is also unknown but likely reflects focal suppression of inflammatory cytokines and inhibition of fibroblast proliferation.⁶² Despite widespread consensus on its efficacy, few studies have objectively evaluated intralesional steroid treatment. The few studies that do exist suggest response rates well over 50%. However, these studies are limited by small sample sizes and unclear evaluation criteria.^{63,64} In one such study, multimodality therapy combining steroid injections with surgery improved response rates to 95% with no recurrence of scarring.⁶⁵ However local side effects from steroid injection include pain, skin atrophy, telangiectasias, and dyspigmentation, demanding careful application.

Pulsed-dye laser and other wavelength-specific lasers have been used effectively to treat hypertrophic scars for many

years. Though the mechanism of action is unknown, one hypothesis suggests that laser absorption by hemoglobin results in capillary ablation and reduced perfusion. The heat generated may also cause dissociation of disulfide bonds with collagen fiber realignment.⁶⁶ However, definitive conclusions have been hampered by small sample size, short-term follow-up, and lack of adequate controls. Review of the dermatologic literature suggests some efficacy when lasers are used as a monotherapy, especially in symptomatic relief of pruritic and erythematous lesions.⁶⁷ While ablative CO₂ and argon lasers have fallen out of favor in treating proliferative scars due to high recurrence rates, newer high-energy pulsed CO₂ and Er:YAG lasers are under investigation and show promise in the treatment of atrophic scars.⁶⁸ Larger-scale studies with long-term results are needed to further delineate the role of laser therapy in scar management.

Topical treatments for hypertrophic scars offer the advantage of convenience. Unfortunately, an effective topical therapy has not yet been developed. Over-the-counter remedies, including vitamin A, vitamin E, and onion extract, have failed to show conclusive evidence in treating or preventing hypertrophic scarring. A prescription topical immunomodulator, imiquimod 5%, has also been investigated for scar treatment and prevention. While early results suggested improved cosmesis in postsurgical scars, subsequent studies have failed to reproduce these effects.^{69,70} Skin-lightening agents containing hydroquinone or retinol can aid in the treatment of hyperpigmented scars.⁷¹ However their use is associated with significant side effects. For instance, in 2006 concern over the carcinogenic risk of hydroquinone prompted a ban of over-the-counter preparations over 2% in the US and a comprehensive ban in Europe.

Treatment of keloid scar

There exists no uniformly successful treatment for keloid scars. Therefore it is essential to discuss the risk of recurrence with potential patients prior to embarking on therapy. Nevertheless, patients frequently seek treatment due to the disfiguring physical and psychological burden of keloid scars. Additionally, symptoms of pain and burning are commonly associated with these scars. In such cases, best practice guidelines currently emphasize the importance of multimodal therapy. Even so, appropriate goals must be set and the patient must be made aware that lesions can redevelop or even worsen on recurrence. Currently the only two viable treatment options for mature keloids are to either (a) monitor the scars routinely, or (b) to excise them and administer adjuvant therapy. Excision and primary closure alone invariably results in recurrence.

Adjuvant therapies for keloids include steroid injection, radiation, cryotherapy, laser, and antitumor or immunosuppressive agents. In general, the first line adjuvant is intralesional corticosteroid injections. Steroids have also demonstrated synergistic benefits when utilized with other modalities such as laser, radiotherapy, and cryotherapy. Triamcinolone acetonide at 10 mg/mL is generally tried initially, and if no response occurs, a 40 mg/mL concentration is attempted. Injection into the dense scar is often painful and associated with risk of infiltration into the surrounding normal tissue. Early, rapidly proliferating lesions respond best to steroid injections whereas slowly growing, mature keloids

respond poorly. Intraoperative and postoperative intralesional steroid therapy following excision has been shown to reduce recurrence rates to below 50%.^{64,72}

A short course of low-dose (20 Gy) radiotherapy to the keloid excision wound immediately after excision has been shown in numerous retrospective studies to reduce the rate of recurrence.^{73–75} A more recent prospective study, however, found recurrence rates of 72% at 1 year following excision and radiotherapy.⁷⁶ The immediate and long-term risks of radiation therapy, including the potential for malignant transformation, demand further study. Nonetheless, radiation therapy may reasonably be considered in adults with lesions refractory to other modalities.

Cryotherapy is a low-cost and effective method of treating select keloid scars. In multiple retrospective series, complete flattening or greater than 80% volume reduction occurred in 73–85% of lesions treated with liquid nitrogen.^{77–79} Early lesions of less than 1–2 years' duration appeared to have more favorable results. A subsequent prospective study examining cryotherapy of both hypertrophic and keloid scars found an even greater response with hypertrophic scars.⁸⁰ In this study, a good to excellent response was found in 78.9% of hypertrophic scars versus only 50.9% of keloids. Interpretation, however, is limited by vague evaluative criteria. Though the mechanism is unknown, the effects of cryotherapy appear to be synergistic with steroid injection.^{81,82} Yet despite its potential efficacy, cryotherapy has been limited to treatment of small lesions due to adverse side effects such as pain, blistering, lengthy wound healing, skin atrophy, and near-universal dyspigmentation.

As with other modalities in scar treatment, critical evaluation of lasers in keloid treatment has been complicated by small studies with vague diagnostic criteria, inconsistent evaluation and lack of long-term follow-up. Additionally, the multitude of laser types and treatment algorithms complicates direct comparative study. A 1995 study in *The Lancet*, for instance, found decreased pruritus and scar height with pulsed-dye laser treatment but did not distinguish keloid from hypertrophic scar and had follow-up limited to 6 months.⁸³ Though lasers have been utilized clinically for scar treatment for nearly 20 years, prudent use is best advised pending further study. Our experience has been favorable when combining pulsed-dye laser with intralesional steroid injection for keloids.

In summary, while there is yet no single modality completely effective in keloid management, multimodality approaches offer some promise. Current treatment algorithms promote the use of corticosteroids, silicone sheeting, and compression garments as first-line therapy, especially in small, early keloids.³⁸ Large, recalcitrant keloids can carry significant morbidity and are very challenging to treat. Optimal management may include surgery, steroids, radiation, or other modalities and are best performed by a surgeon or center with a focus on keloid treatment.

Emerging treatments

A promising new therapeutic modality is the local delivery of antitumor and immunomodulatory drugs for the treatment of keloid and hypertrophic scars. The use of immunomodulatory agents such as TGF- β modulators, interferons (IFNs),

5-fluorouracil (5-FU), and bleomycin allow us to exploit our growing understanding of scar biology to offer new solutions to age-old problems. While the body of data is still small, early evidence suggests that these drugs have potential for the safe and effective treatment of excessive scarring.

TGF- β s are profibrotic growth factors that attract and stimulate fibroblasts to increase collagen synthesis and decrease ECM breakdown. Changes in TGF- β activity have been linked to fibrotic diseases of the kidney, lung, and heart. A robust body of literature implicates the TGF- β family as a major determinant of scar morphology.^{84,85} This increased knowledge of signaling pathways and TGF- β isomers has been translated into new therapeutic avenues for exploration. For instance, initial phase I/II trials of prophylactically injected recombinant TGF- β 3 have demonstrated an improvement in the appearance of scars.⁸⁶

IFNs are anti-fibrotic cytokines that suppress the formation of collagen.⁸⁷ Trials of intralesional injections of IFN- α 2b and later IFN- γ as both monotherapy and postsurgical adjuvant therapy have yielded positive results. An early study found reduced keloid recurrence rates of 18.7% with adjuvant IFN- α 2b injection versus 51.2% with surgery alone at a 7 month follow-up.⁸⁸ Subsequent studies, however, have been mixed. Some trials have shown early recurrence when interferons are used as monotherapy while others indicate benefits with combined therapy.^{89,90} Nevertheless, targeted therapy with IFN continues to be alluring from a biochemical standpoint, and deserves further investigation.

Antineoplastic agents 5-FU and bleomycin are additional promising pharmacologic candidates for treatment of pathologic scarring. Small RCTs have built upon the experience of large clinical series to provide preliminary evidence for the efficacy of 5-FU in keloid treatment.^{91–93} In one study, side-by-side application of 5-FU and steroid injections on median sternotomy keloids suggested equal efficacy for 5-FU without the side effects of skin atrophy, hypopigmentation, or telangiectasia seen with steroid treatment.⁹⁴ Though not yet fully understood, the effects of 5-FU may be mediated in part through interference with the TGF- β signaling pathway.⁹⁵ Bleomycin, on the other hand, is thought to act by binding DNA and preventing mitosis.⁹⁶ Initial clinical studies from Europe suggest efficacy without systemic toxicity.^{97,98} While results have thus far been favorable for both these agents, larger-scale studies are needed to validate the findings of early small studies.

Scar revision

Introduction

Plastic surgery education and techniques enable practitioners to offer surgical, nonsurgical, and combined treatment modalities to patients with scars. Treatment is therefore based on understanding of underlying pathology rather than limited to a certain tool or device. For the most disfiguring and debilitating scars, surgery is often a necessary component of therapy, if not the only effective therapy. After careful analysis of a scar's characteristics (morphology, maturity, distortion of tissues) and appropriate application of noninvasive measures,

the plastic surgeon can then turn to an array of surgical tools to treat a difficult scar.

Indications

Patients seek scar revision for a multitude of reasons. As discussed earlier, scars carry both physical and psychologic implications. Understanding what role these factors play in a patient's desire for treatment is important in setting and reaching patient expectations.

Scars eliciting physical symptoms should be examined carefully. Patients will often report discomfort and tightness as a result of scar contraction. An exquisitely painful scar should be examined for Tinel's sign, which may suggest entrapment of a cutaneous nerve. Excision or repair of a neuroma is often an important part of scar revision. Scar contractures across joints, frequently seen in burn patients, can result in limited functionality and reduced range of motion. In such cases, treatment should be directed at restoration of function and be carried out in conjunction with aggressive physical therapy to prevent recurrence.

Disfiguring scars can cause significant personal and social burdens. The surgeon should be sympathetic and nonjudgmental as these scars may be reminders of past trauma and current hardship. Administering care alongside a mental health professional can help distinguish and address complicating psychological issues. For the surgeon, extra care must be taken in these circumstances to confirm realistic expectations and reinforce the goals of care.

Timing

Timing of scar revision should reflect an assessment of scar maturity and an understanding of the underlying biology. A soft supple mature scar is the ideal starting point from which to consider revision. Immature scars contain the fragile blood vessels of neovascularization, which may bleed excessively during surgery. In addition, the tissue in and around immature scars is more edematous and less mobile, complicating local tissue rearrangement. Tissue primed for scar revision should be maximally mobile and soft.

Surgical timing should therefore be based on clinical exam, though some suggest delay for at least 18 months. Interval exams should be used to monitor a scar until one can be certain of maturity. Any uncertainty in scar maturity should prompt the physician to wait longer. This can often be difficult in patients who are eager for a solution. Nonoperative management such as massage and silicone sheeting should be offered to the patient during this period as it can help maximize outcome. A patient's compliance with nonoperative measures can also help serve as a measure of his or her motivations and expectations. This can also be a time to build a relationship of trust between the patient and physician. Those eager to proceed may not have realistic expectations and should be counseled accordingly. Patients should be advised that early revision will increase the risk of complications and will reset the clock on wound healing and scar maturity.

Hypertrophic scarring can be thought of as a chronic inflammatory condition. Early surgery is all the more plagued by immobility and bleeding. Unless planning to excise the

entire scar, surgery should be deferred until scar maturity is achieved. This can often take longer than with normotrophic scars and should again be dictated by clinical exam. Dr. Mil-lard's principle "When in doubt, don't!" bears stressing.¹

Planning

In addition to timing, several other factors are important to consider when planning for surgical scar revision. For complex reconstructions involving multiple areas, management is best directed at larger areas initially. For instance, burn scars involving the head and neck should start with resurfacing of the cervicofacial region before addressing the ectropion.

Surgeons must also determine if each scar is best treated by single or multistaged revision. Single-staged operations include both simple direct excisions and more complex soft-tissue rearrangements. Unless an initial wound was widened due to infection and dehiscence, direct excision alone is rarely effective. When applicable, however, preoperative suturing and on-table tissue expansion can be used to decrease tension on a wound after direct excision. Undermining and advancement of skin edges similarly allow for reapproximation without tension. This can be performed asymmetrically to change the degree of tension and deformity in neighboring tissue. Subsequent use of a tension off-loading dressing can further minimize scarring.³⁷

Serial excision and tissue expansion are staged strategies for scar revision. While seemingly simplistic, staged serial excisions of scars may provide the best results (Fig. 14.8). Two or three serial excisions of a large scar may accomplish what is hazardous or even impossible in a single stage operation. Serial excision is accomplished by circumferentially excising the margin of a scar, then undermining and advancing bordering normal tissue. The pliability of the normal tissue should be assessed before making the incision. This will dictate how much scar is safe to excise and timing of subsequent stages.

Tissue expansion is an alternative method for staged scar revision. This procedure enables the body to grow extra skin for use in reconstruction through the placement of expanders under the skin. Tissue expansion has been especially valuable in scalp reconstruction of patients with burn alopecia, though it does carry the additional risk of infection associated with implant placement and requires two procedures for insertion and subsequent removal.

Scar release

Scarring is a three-dimensional process that often extends from superficial to deep tissue. Scar contracture in deep layers can result in puckering and tethering of the overlying tissue. This can occur even in the absence of superficial injury. Fat necrosis following blunt tissue trauma, for instance, can result in a concave skin defect without laceration. Treatment of tethered scar requires release from the underlying tissue and sometimes interposition of muscle or fascia. Soft-tissue fillers, fat autograft, and acellular dermis have all been used successfully to fill depressed scars, although long-term data are lacking.^{99–101}

Acne scarring requires special consideration as the multiple pitted scars of "ice-pick" acne can be disfiguring and result in



Fig. 14.8 (A–C) Serial excision.

considerable psychological stress for the patient. Mild to moderate acne scars may benefit from resurfacing procedures such as those using CO₂ laser or chemical peels to even out contour deformities.¹⁰² More serious acne scars, however, require formal excision to achieve adequate depth. Focal excision with release of tethered tissue can be extremely effective but should first be applied to one or two test lesions to assess patient-specific results.

Principles of tissue rearrangement

The surgical approach to scar revision should be guided by the same principles outlined for scar prevention. These include atraumatic technique, tensionless closure, and proper skin eversion. Scar revision that involves tissue rearrangement, discussed further below, also requires consideration of anatomic landmarks and lines of tension. Restoration of anatomic landmarks such as the vermillion border, eyelid position, or alar base should take priority over minimizing scar characteristics.¹ The use of local flaps in the face to prevent distortion of anatomic landmarks is an example of this principle. In this instance, the larger scar of a flap is preferred when local tissue recruitment would result in deformity of facial landmarks. Scar revision should similarly focus on restoring anatomic structures to their correct location.

Scars should be hidden in the resting lines of skin tension. Presented originally in 1861, Karl Langer's eponymous "lines" resulted from examination of vertical wounds left by circular stab marks into a cadaver.¹⁰³ Reorientation of a scar to these lines allows for the least tension across a wound.¹⁰⁴ This is achieved in scar revision surgery via tissue rearrangement techniques such as Z-plasty. The lines of resting tension form the basis for the aesthetic units and subunits that dictate facial surgery.^{104,105} The face, however, is dynamic and patients should be cautioned that scars may become more apparent with changes in expression.

Scar elongation and irregularization are other principles that reflect consideration of tension lines caused by the scars

themselves. Myofibroblasts in a mature scar can cause scar contracture within the axis of the scar. A long, straight scar will result in uniform contracture in one axis, causing greater deformity in the surrounding tissue and greater depression of the scar. This tight scar can lead to limitations in movement. Furthermore, the change in contour may be aesthetically displeasing. Thus, in addition to reorienting the scar, local tissue rearrangement techniques break up the length of the original scar by incorporating neighboring tissue. A longer scar relaxes the pull on each end of the scar towards the center of the scar. Contractile forces are displaced into the axis perpendicular to the length of the scar. Multiple applications of this technique result in an irregular scar, wherein contractile forces are dispersed into multiple axes. This, in turn, results in less tissue deformation and a more easily camouflaged scar.

Scar revision techniques

Local tissue rearrangement requires an understanding of tissue properties, careful planning, and meticulous technique. When applied successfully, these simple but fundamental principles embody the art of plastic surgery and enable the surgeon to attain goals of scar reorientation, elongation, and irregularization necessary for effectively addressing difficult scars.

Though some argument exists, the Z-plasty technique can be traced back at least as far as Horner in 1837 and Denonvilliers in 1854.¹⁰⁶ Their procedure for transposing triangular flaps to relieve cicatricial ectropion has evolved over time into the modern Z-plasty. In current nomenclature, Z-plasty refers to transposition of two triangular flaps, usually of equal size and equal angle, into each other's defect.

Planning and performing Z-plasty requires an understanding of geometric principles. The first published mathematical analysis came from Limberg in 1929.¹⁰⁷ Through the Pythagorean theorem he revealed the theoretical gains in length achievable with changes in the angle of the lateral limbs

Table 14.4 Z-plasty gains in length

Angle of lateral limb of Z-plasty	Theoretical gain in length of central limb (%)
30	25
45	50
60	75
75	100
90	120

(Table 14.4).¹⁰⁸ In practical application, however, the elasticity of skin and rigidity of scar create unequal deformation of the central and lateral limbs.¹⁰⁹ This deformation results in lower gains in length *in vivo* than would be expected in theory. Deformational forces are magnified with smaller flaps and with serial Z-plasties. Nevertheless, proper execution of a Z-plasty is essential to accomplishing four fundamental functions: lengthening a scar, breaking up a line, moving tissue, and obliterating or creating a web or cleft (Box 14.3).¹¹⁰

Z-plasties have been further divided into simple, planimetric, skew, and multiple. The simple or stereometric Z-plasty has two flaps of equal angle and length (Fig. 14.9). Traditionally, these flaps are raised at 60° as this angle offers the best balance between elongation in the axis of the scar and the creation of tension forces pulling perpendicular to the scar. Last-minute flap revisions can be avoided by incising and transposing one flap to determine excursion accurately *in vivo* before cutting the second flap.

The planimetric Z-plasty is a variation of the classic Z-plasty that maintains the flaps in the same plane (Fig. 14.10).¹¹¹ By minimizing the amount of rotation and excising redundant tissue, this flap design avoids the contours and depressions created by simple Z-plasty. Flaps may theoretically be designed with lateral limb angles ranging from 60° to 90°, though most often they are planned at 75° angles. The planimetric Z-plasty is ideal for scar releases on flat surfaces where lengthening is the primary objective and contour deformities would be suboptimal.

Skew Z-plasties have lateral limbs departing at different angles from one another (Fig. 14.11). This flap has been suggested when anatomic landmarks mandate asymmetric movement of one flap. Furnas and Fischer's topographic study in dogs revealed that the narrow flap transposed easily but was likely to form a "dog ear", while the wider flap was difficult to transpose and caused more stretch at its base.¹⁰⁹ This is counterintuitive to some degree as the narrow flap has to travel through a larger arc of rotation to traverse the wide flap. For this reason, deformational forces created by skew Z-plasty flaps can be difficult to predict and its use should be avoided.

BOX 14.3 The four fundamental functions of Z-plasty

1. To lengthen a scar
2. To break up a straight line
3. To move tissues from one area to another
4. To obliterate or create a web or cleft

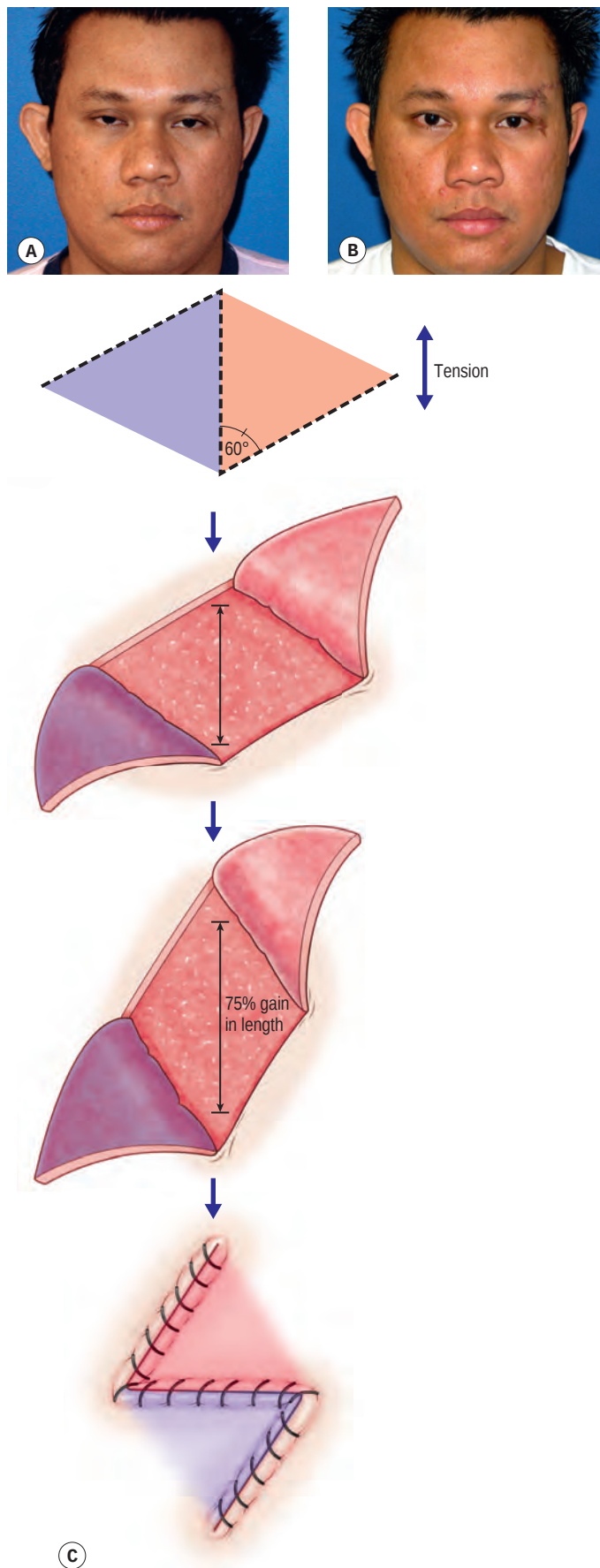


Fig. 14.9 (A–C) Simple Z-plasty.

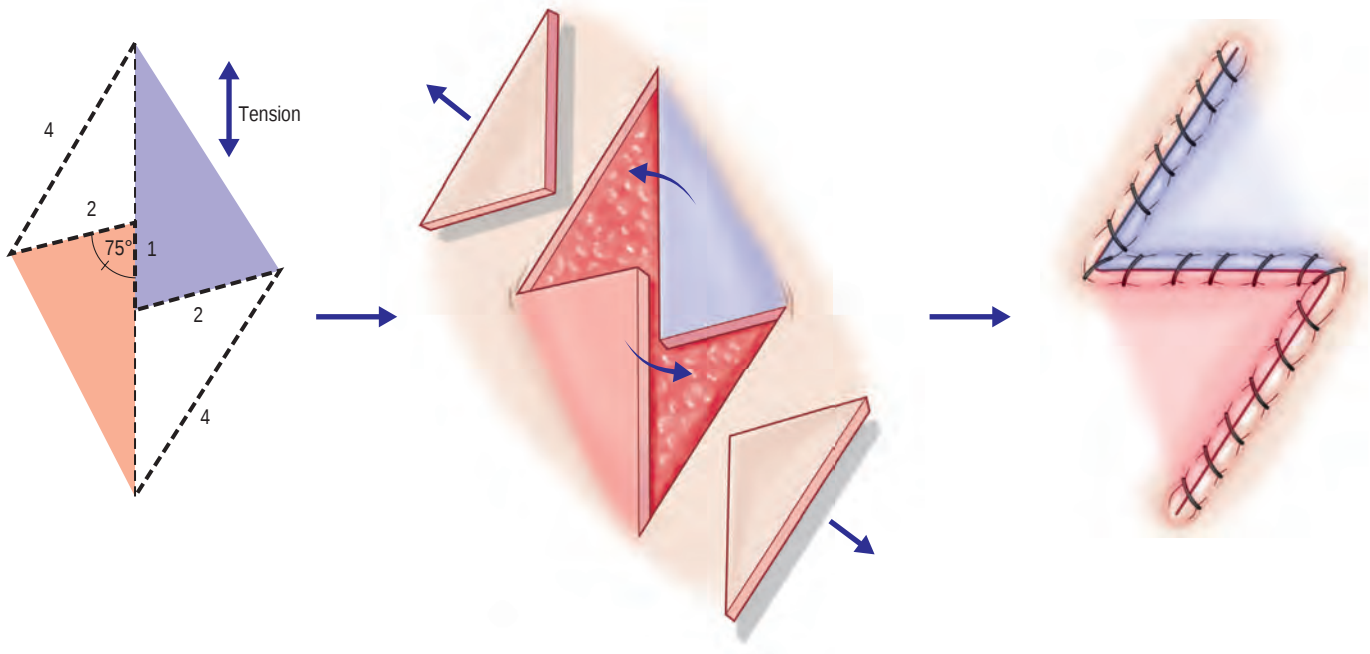


Fig. 14.10 Planimetric Z-plasty.

Multiple-flap Z-plasty refers to multiple Z-plasties along a scar length as well as Z-plasties designed with more than two flaps (Fig. 14.12). When performing multiple Z-plasties in series, the previous Z-plasty exerts deformational forces on the tissue of the next Z-plasty, further limiting the actual gain in length. A single large Z-plasty at a specific angle will therefore create more length than multiple small Z-plasties at that same angle. A large Z-plasty, however, is not always in keeping with the aesthetic and functional goals of a scar revision. Numerous Z-plasties utilizing multiple flaps have been devised. Among them, the Limberg's four-flap and Mustarde's "jumping man" five-flap Z-plasties are frequently used for release of first-web-space contractures (Fig. 14.13).^{107,112}

Regardless of design, care must be taken to widen the tip of flaps to avoid tip necrosis.¹¹³ The thickness of flaps is

dictated by the quality and location of the tissue. Scars often have distorted and unreliable blood supply, therefore thicker flaps are necessary. In unscarred tissue, care must be taken to elevate the subdermal vascular plexus to include the cutaneous microvasculature in the flap.

Other scar revision techniques include V-Y and Y-V advancement flaps, W-plasty and geometric broken line. V-Y and Y-V advancement flaps allow for the incorporation of adjacent tissue without the threat to vasculature necessary for Z-plasty (Fig. 14.14). These flaps are not transposed and therefore do not require undermining. Like Z-plasties, these flaps can be carried out in tandem through careful flap design.

W-plasty and geometric broken line are techniques for scar irregularization (Figs. 14.15, 14.16).¹¹⁴ W-plasty uses a zigzag pattern excision of the scar followed by reapproximation of

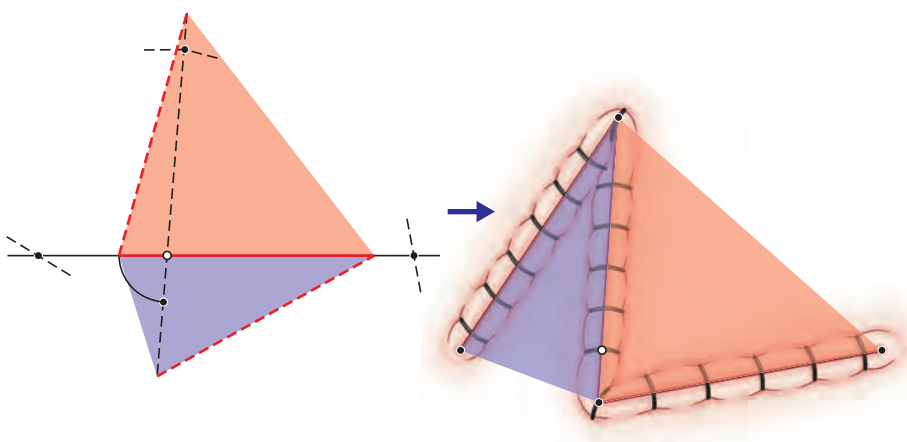


Fig. 14.11 Skew Z-plasty. (Reproduced from Furnas DW. Transposition of the screw z-plasty. *Br J Plast Surg.* 1966;19:88–89.)



Fig. 14.12 (A–C) Multiple Z-plasties. (With permission from Dr. Shelly Noland.)

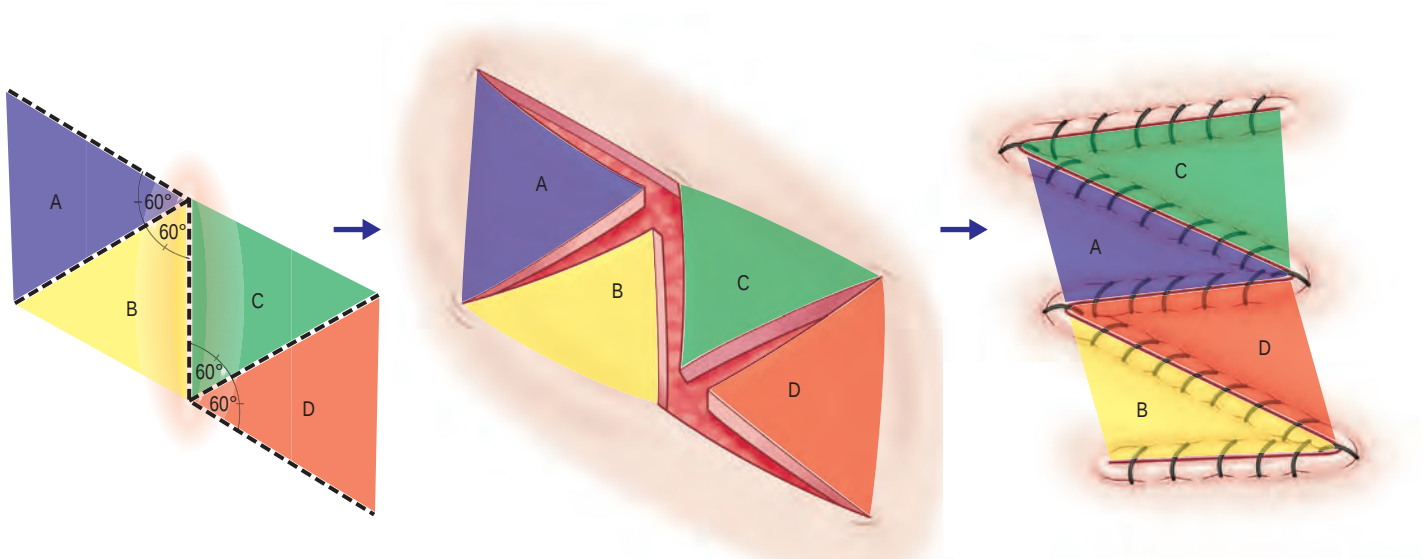


Fig. 14.13 Four-flap Z-plasty.

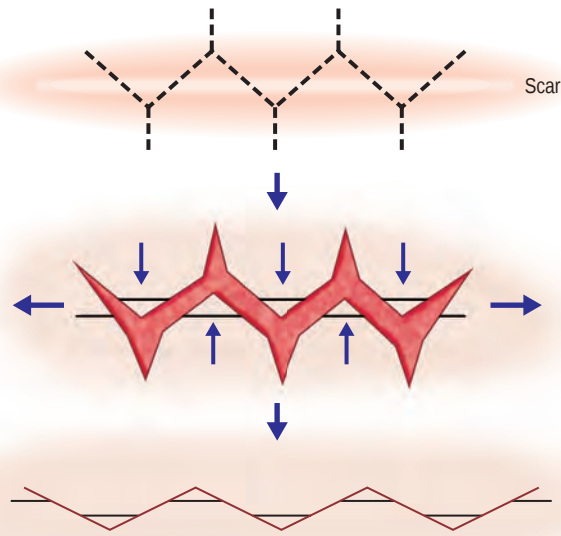


Fig. 14.14 V-Y and Y-V advancement flaps.

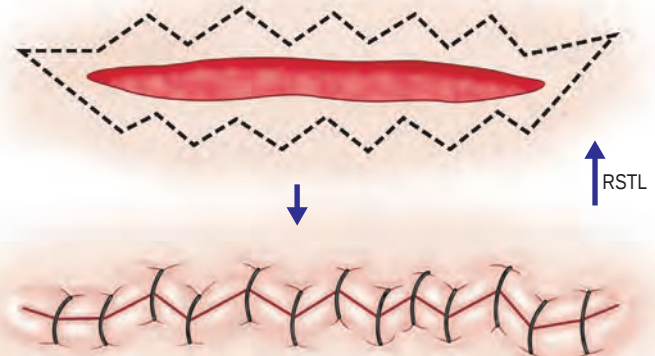


Fig. 14.15 W-plasty. RSTL, relaxed skin tension lines.

small interdigitated limbs. There is no elongation of the scar and tissue is removed, therefore a net increase in tension is produced in the axis perpendicular to the scar. In contrast, Z-plasty trades relaxation in the axis of scar for tension perpendicular to the scar, resulting in no change in overall tension. Albert F. Borges has suggested W-plasty as a good revision technique in facial scars that are not in the resting lines of skin tension and do not have excessive tension across them.¹¹⁴

Lastly, geometric broken line is a refined technique wherein 5–6 mm randomly distributed triangles, squares, trapezoids, and semicircles are incised at the wound edge with reciprocating shapes planned opposite them. However, this technique is challenging and labor-intensive, though it may have some utility in further camouflaging facial scars that cross aesthetic subunits.

Postoperative care and follow-up

Initial postoperative care should be directed towards optimal wound healing, including adequate nutrition, blood sugar control, smoking cessation, and activity precautions. Long-term scar reduction techniques are aimed at prevention and treatment. Following a revision, scar reduction can be achieved through use of a tension off-loading device. Aggressive use of taping, silicone sheeting, compression, and scar massage may also provide modest improvement. More detailed follow-up care should be dictated by patient-specific factors. Regardless of complexity, however, both the patient and physician benefit from long-term follow-up as this provides an opportunity to evaluate the efficacy of any treatment strategies.

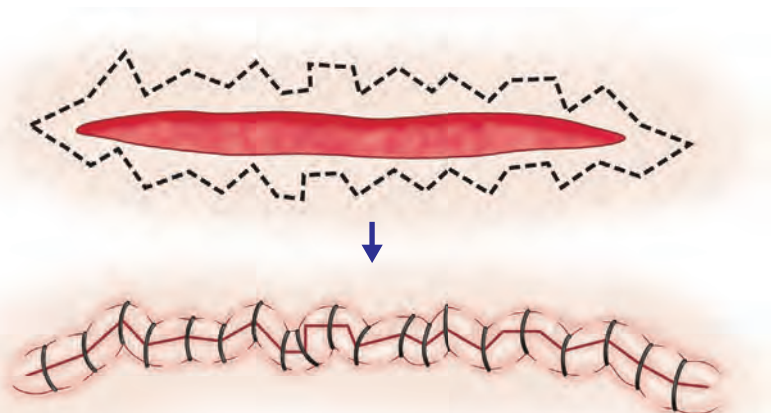


Fig. 14.16 Geometric broken line.



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Skin graft

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SYNOPSIS

- History of skin grafting mirrors many of the important advances of plastic surgery.
- There are complex biologic mechanisms that allow skin grafts to take.
- There are a variety of types of skin grafts that can be selected based on clinical application.
- Technique should be adjusted to avoid most complications.
- There are exciting areas of research that will help minimize donor site size and improve function and appearance of skin grafts.

Skin grafting is a technique for the transfer of cutaneous tissue from one site of the body to another, often to cover large defects. Depending on the thickness of the dermis of graft that is harvested, skin grafts are defined as full-thickness or split-thickness. See [Fig. 15.1](#), [Box 15.1](#) and [Video 15.1](#) ▶ for a step-by-step guide on how to prepare a skin graft.



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Anatomy and physiology

The skin represents approximately 8% of our total body weight, with a surface area of 1.2–2.2 m². The skin is 0.5–4.0 mm thick and covers the entire external surface of the body, including the walls of the external acoustic meatus and the lateral tympanic membrane. The main function of skin is to protect body contents from the environment, including pathogens, temperature, and excessive water loss. Insulation, temperature regulation, sensation, immune function, and the synthesis of vitamin D are all critical functions of the skin. Skin loses regenerative capacity when lesioned down to the lower dermis and results in scar tissue when injured.

Epidermis

Skin has a complex three-dimensional structure characterized by two overlapping layers, the epidermis and the dermis. The epidermis, as the nervous system, derives after gastrulation from the neuroectoderm. Epidermis is the outer or upper layer of skin, which is a thin, semitransparent, water-impermeable tissue, consisting primarily of keratinocytes. These cells form a multilayered keratinized epithelium, similar to a wall of bricks. The basement membrane separates the epidermis from the dermal tissue and consists of a protein structure produced by basal keratinocytes. Basal keratinocytes are partially differentiated stem cells of the epidermis that provide the proliferative and regenerative capacity of the skin epithelium. The epithelium is metabolically active and continuously self-renews to maintain an efficient barrier function. Cellular homeostatic regulation is, as a consequence, very important: too little proliferation would bring a loss of barrier and excessive activity to hyperproliferative disorders, such as psoriasis. Homeostasis is granted by the basal epidermal cells, which periodically cycle, executing their program of terminal differentiation, a process that takes approximately 28 days. The differentiation of the keratinocytes is characterized by the progressive production of alpha-keratin, with migration towards the surface until the cells lose their intercellular connections (desmosomes), die, and become corneal lamina.

During this process, called cornification, basal keratinocytes produce tonofilaments (precursor of keratin) and then transform into the stratum spinosum as the desmosomes stretch the cells into spikes visible with a microscope. In the plasmalemma, the tonofilaments are connected to the desmosomes. Cells next start to produce keratohyalin, which aggregates in dense and basophilic granules, giving the name to the stratum granulosum. In these granules a histidine-rich protein, profilaggrin, becomes progressively filaggrin, which ultimately acts as a glue to keep keratin filaments together once the cells die and the cell membrane degrades.

As the cells divide and move up through the epidermis they eventually transform into the stratum corneum, a layer

Historical perspective

Skin is the largest human organ, covering 1.7 m² in the average adult. It serves as an essential barrier with mechanical, immunological, and aesthetic functions. Skin transplantation has long fascinated humans and there is evidence that skin grafts were performed in India as early as 1500 BC for traumatic nasal amputation. Modern science has taught us much about the anatomy and physiology of skin.

Gaspare Tagliacozzi, one of the first reconstructive surgeons (1545–1599),¹ described pedicled skin flaps from the arm for nasal reconstruction in patients. Two centuries later research was conducted by Giuseppe Baronio (1750–1811), who performed and published for the first time skin grafts in a lamb (*Degli innesti animali*, 1804).² Jonathan Warren in Boston and Joseph Pancoast in Philadelphia were among the first to perform and describe autologous full-thickness skin grafting in humans using the arm as a donor site. Paul Bert, a French politician, showed in his thesis that skin graft survival is only possible if blood vessels of the recipient site are able to revascularize the graft. His work popularized this technique.³ For the techniques, Reverdin, a French student, described harvesting skin islands with the scalpel tip with transfer to a first web space wound.⁴ He discovered that these skin islands not only temporarily covered, but also actively stimulated, wound healing. Reverdin's work was rapidly accepted and performed by multiple surgeons in the US. The term "dermoepidermoid"

graft was introduced by Leopold Ollier (1830–1900), who also first used the split-thickness skin graft (STSG) to close entire wounds.⁵ He noticed that healing was achieved faster and wound contraction was minimized. The German surgeon Carl Thiersch (1822–1895) further developed the technique of skin grafting and introduced the concept of wound bed preparation by removing granulation tissue to achieve a clean wound bed to facilitate graft revascularization. The English ophthalmologist, John Reissberg Wolfe (1824–1904), from Glasgow, published the use of a full-thickness skin graft for ectropium correction.

With the development of skin harvest techniques the number of publications reporting clinical results of skin grafts increased exponentially. Later, James Carlton Tanner (1921–1996) revolutionized burn surgery by the introduction of meshing to expand skin grafts in order to cover larger wounds with minimal donor site morbidity.⁶

Reverdin's technique was modified by John S Davis (1872–1946), who elevated the skin with a needle in 1914 to facilitate harvesting, a technique that he called "pinch graft".⁴ In 1920 Ricardo Finochietto (1888–1962) developed a knife to elevate larger skin areas manually by controlling the thickness of the skin graft. Ten years later, the invention of the shave blade by Humby further facilitated skin harvest.

The introduction of the mechanical dermatome of Padgett-Hood and Reese in 1940 and 8 years later the development of the electric dermatome by Harry Brown significantly facilitated skin harvest of large surfaces in a controlled manner.

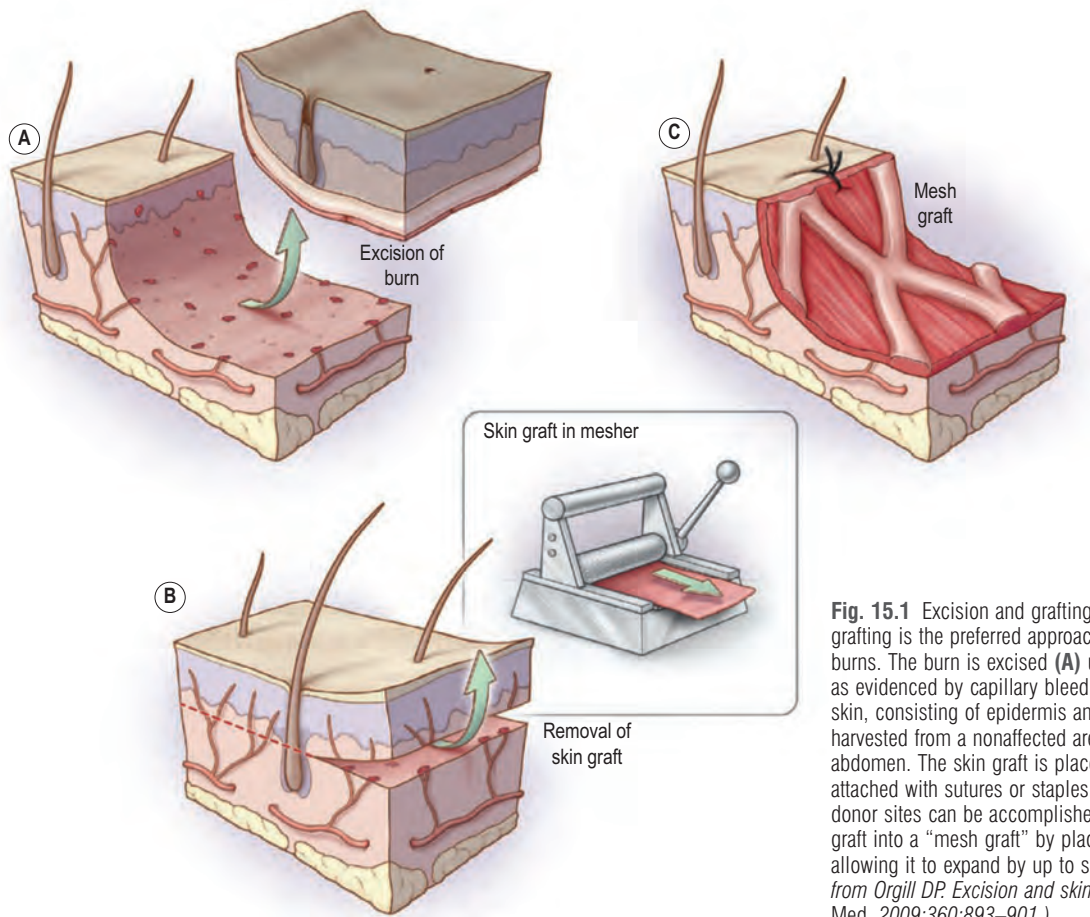


Fig. 15.1 Excision and grafting. A combination of excision and grafting is the preferred approach for the treatment of deep dermal burns. The burn is excised (**A**) until a viable wound bed is reached, as evidenced by capillary bleeding. The graft (**B**) is a thin layer of skin, consisting of epidermis and partial-thickness dermis, which is harvested from a nonaffected area, often the anterior thigh or abdomen. The skin graft is placed over the excised area (**C**) and attached with sutures or staples. Reduction of the size of skin-graft donor sites can be accomplished by making the split-thickness skin graft into a “mesh graft” by placing multiple small slits in the graft, allowing it to expand by up to six times the original area. (Adapted from Orgill DP. Excision and skin grafting of thermal burns. *N Engl J Med.* 2009;360:893–901.)

of dead cells, which ultimately is highly mechanically and chemically resistant due to chemical bonds between lipids and proteins. It is thought that cells die as the increasing proteins in their cytoplasm start to activate lysosomes. The stratum corneum provides an extremely effective barrier layer to keep water in and microorganisms out.

Also contained within the epidermis are melanocytes, Langerhans cells, Merkel cells, and sensitive nerves. Around

10% of the epidermal cells are represented by melanocytes, which derive from the neural crest. These complex dendritic cells produce melanin granules (contained in the melanosomes) that are then transported through dendrites into keratinocytes, providing color to the skin and protecting basal epithelial nuclei from ultraviolet damage. Melanocytes are anchored to the basal lamina by hemidesmosomes, but do not have desmosomic connections with other cells.

BOX 15.1 How to perform a skin graft

- Prepare the wound bed for grafting (debridement and hemostasis)
- Estimate the needed skin graft size
- Clean the donor site from any residual disinfection (i.e. Betadine)
- Apply paraffin on the donor site
- Set the dermatome at 0.2 mm thickness
- Stretch the donor site skin
- Apply the dermatome at a 45° angle and apply light pressure
- Slide the dermatome along the skin while an assistant is lifting the skin graft with two forceps
- Lift the dermatome upwards when the desired size of graft is obtained
- Dress the donor site with Vaseline gauze, dry gauze and bandages
- Fix the bandage generously to the skin (e.g. thigh) to avoid sliding down of the dressing
- Spread evenly the graft (dermal site of the graft upwards) on a dermal carrier (rough surface of the carrier upwards) of the desired size (1 : 1.5, 1 : 3, etc).
- Pass the graft through the graft mesher paying attention that it does not detach from the dermal carrier
- Apply the graft on the recipient site by sutures, surgical staples or fibrin glue
- When indicated apply a bolster dressing by placing Vaseline gauze on the skin graft, followed by a cotton sponge impregnated with Betadine or saline solution and tight sutures (4/0 nylon or polypropylene) from the opposite wound margins together at the center of the defect
- First dressing change should be around 5–7 days post-op

Langerhans cells are the immune cells of the epidermis and are important in generating a response to foreign agents, playing an important role in allograft rejection and contact dermatitis. These cells are situated in the stratum spinosum and, with long dendrites, slide between epithelial cells, without desmosomic connections to them. Langerhans cells share several features with macrophages of connective tissues.

Merkel cells are commonly found in the epidermis of palms, soles, nail beds, oral and genital areas. Merkel cells act as mechanoreceptors and thus are responsible for neurosensory transmission. These cells reside in the basal layer of the epidermis, often protruding into the dermal layer like nails. Merkel cells are connected by desmosomes to the neighboring cells.

Skin adnexal structures are epidermal derivatives that invaginate into the dermis with a lining of epithelial cells. They include hair follicles, sweat and sebaceous glands. These structures provide the basis for re-epithelialization following the harvest of a split-thickness skin graft (STSG).

Sensitive nerve supply to the skin is rich and extends through the basement membrane into the epidermis. Nerve fibers also go to skin adnexal organs that allow hair to become erect and sweat glands to secrete.

Dermis

The dermis is a tough fibrous layer that provides the mechanical features of the skin. It is composed primarily of collagens, glycosaminoglycans, and elastins. Skin grafts without the dermis result in a closed but often unstable skin. Grafting a part of the dermis is therefore very important to consider in terms of functionality of the future skin.

The upper part of the dermis has a particular architectural organization that is called papillar and contains blood vessels and nerve fibers. The papillar layer of dermis consists of fine collagenous fibers that form an undulating interface with the overlying basement membrane and epidermis. This structure increases the contact area between dermis and epidermis, allowing for maximal mechanical stability of the two layers and an exchange surface for diffusion. Deeper, we find the reticular dermis, with increasingly thicker collagenous fibers (mainly of type I) as we move toward the subcutaneous tissue. The reticular dermis has larger collagenous fibers with substantial strength. The mechanical properties of the dermis are critical to allow movement while providing stability and protection from mechanical trauma. The dermis is remarkably self-healing, mainly due to the presence and activation of myofibroblasts following injury.

Blood vessel supply of the skin

Dermal vascularization is particularly important, as blood vessels are not directly present in the relatively more metabolically active epidermal layer, glands, and hair follicles. Blood vessels set up a rich superficial plexus just underneath the basement membrane in the papillary dermis, facilitating nutrient transport to the epidermis. The blood vessels in the papillary dermis are arranged in the papillary plexus, with a rich network of capillaries in the papillae, which come in close contact with the epidermis. Deeper in the dermis is the reticular plexus from which small vessels distribute to the subcutaneous and deep dermal tissues to vascularize adnexal organs,

including the hair follicle bulb. Arterial capillaries generate venous plexi, which have the same distribution of arterial vasculature. In the deep layers of dermis it is possible to find several arteriovenous anastomoses, particularly at the extremities (hands, feet, ears), where they exhibit strong muscular sphincters. The function of these structures is mainly under the control of the visceral nervous system, with the main function of thermoregulation and intravascular volume redistribution.

Blind-ended lymphatic structures are present in the dermis from where they connect to the reticular plexus and to larger vessels in the subcutaneous tissue. In this region, lymphatic vessels are larger, with valves, and drain into deeper lymphatic vessels called regional collectors. In the skin the lymphatic drainage is very active with multiple interconnections enabling lymphatic exchange. Circumferential skin and subcutaneous damage can therefore lead to problematic lymphatic stasis in extremities or in the genital area.

Stem cells and regeneration of skin

Basal epithelial keratinocytes are the committed stem cells of the epidermis. Constant self-renewal provides a new protective layer at the skin surface.⁷⁻¹² Hair follicles contain multipotent stem cells that are activated upon the start of a new hair cycle and upon wounding to provide cells for hair follicle and epidermal regeneration. In the hair follicle, stem cells reside in the bulge area. Bulge cells are relatively quiescent compared with other cells within the follicle.^{9,10} However, during the hair cycle, bulge cells are stimulated to exit the stem cell niche, proliferate,¹³ and differentiate to form the various cell types of the hair follicle.¹⁴ In addition, bulge cells can be recruited during wound healing to support re-epithelialization.^{15,16}

The relative importance and exact contribution of bulge cells to wound healing are currently unknown as areas of the body such as the palms and soles that lack hair follicles still exhibit normal healing.

Hair follicles

Hair differentiates in a craniocaudal direction, 9 weeks after gestation, as mesenchymal cells populate the skin to form the dermis. Specialized cells in the dermal layer stimulate epithelial cells to proliferate and migrate downward into the epidermis, forming hair canals. The complete developed hair follicle contains an ectoderm-derived matrix and an underlying mesoderm-derived follicular papilla. There are three bulges that attach to the hair bulb. At the base the erector muscle develops, the middle part gives rise to the sebaceous gland, and the superficial bulge develops into an apocrine unit (Fig. 15.2).

Histological structures of the hair follicle can be divided as follows. The part that reaches from the entrance of the hair follicle into the skin to the apocrine gland is the infundibulum. The zone between the apocrine gland and the sebaceous gland is referred to as the isthmus. The stem of the hair follicle is located between the sebaceous gland and the base of the erector muscle. The bulb is the deepest part of the hair follicle and contains the follicular matrix and papilla. This part is growing and regenerates the hair after injury. If the bulb is lesioned the hair will not recover from injury.

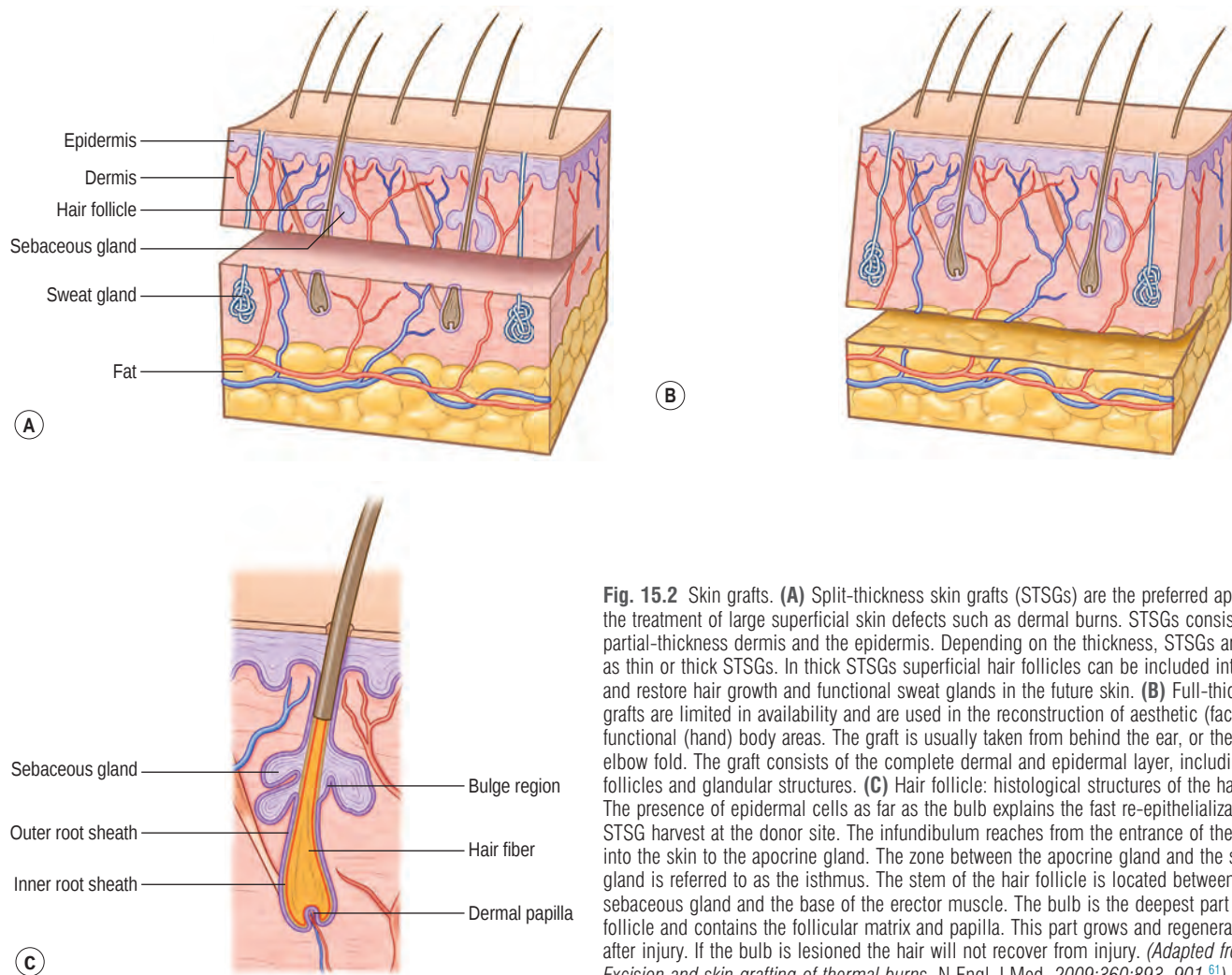


Fig. 15.2 Skin grafts. **(A)** Split-thickness skin grafts (STSGs) are the preferred approach for the treatment of large superficial skin defects such as dermal burns. STSGs consist of the partial-thickness dermis and the epidermis. Depending on the thickness, STSGs are referred to as thin or thick STSGs. In thick STSGs superficial hair follicles can be included into the graft and restore hair growth and functional sweat glands in the future skin. **(B)** Full-thickness skin grafts are limited in availability and are used in the reconstruction of aesthetic (face) or functional (hand) body areas. The graft is usually taken from behind the ear, or the inguinal or elbow fold. The graft consists of the complete dermal and epidermal layer, including hair follicles and glandular structures. **(C)** Hair follicle: histological structures of the hair follicle. The presence of epidermal cells as far as the bulb explains the fast re-epithelialization after STSG harvest at the donor site. The infundibulum reaches from the entrance of the hair follicle into the skin to the apocrine gland. The zone between the apocrine gland and the sebaceous gland is referred to as the isthmus. The stem of the hair follicle is located between the sebaceous gland and the base of the erector muscle. The bulb is the deepest part of the hair follicle and contains the follicular matrix and papilla. This part grows and regenerates the hair after injury. If the bulb is lesioned the hair will not recover from injury. (Adapted from Orgill DP. Excision and skin grafting of thermal burns. *N Engl J Med.* 2009;360:893–901.⁶¹)

Follicles can be found in different phases: anagen (proliferating phase), catagen (regression phase), and telogen (resting phase).

Although no new hair follicles are made postnatally, the lower portion of the hair follicle regenerates in order to produce new hair. Some of this capacity has been linked to the presence of multipotent epithelial stem cells. These cells can be found in the lowest permanent portion of the hair follicle – the bulge.¹³ Bulge stem cells are activated during the transition from telogen to anagen, to restart hair growth.

Glandular structures

Sebaceous glands are small saccular structures residing throughout the dermis, but are more common in thicker areas. These glands produce lipid-rich sebum on the surface of the skin and around the hair shaft. The function of sebum is still partially unknown but probably is linked to protection of the hair and contributes to the impermeabilization of the skin, giving protection from stings and parasites. Sebaceous glands are particularly large on the face, trunk, shoulders, and genital and perianal regions. When excessive quantities of sebum are produced – such as during puberty – the duct can be obstructed and ultimately may become infected or form cysts.

Sweat glands are divided into eccrine and apocrine glands. There are numerous eccrine glands in every region of the body except the tympanic membranes, lips, nail bed, nipples and clitoris. Their body has a glomerular structure and they excrete a clear odorless, hypotonic liquid. The secretion is stimulated mainly by an increase in body temperature, with the exception of some regions, such as palms, face, and axilla, where the main stimulus is emotional.

Apocrine glands are found exclusively in the axillar, perianal, periumbilical, areolar, preputial, scrotal, pubic and vulvar areas. While their structure is similar to that of the eccrine glands, these glands differ as regards the quality of their excretions, which are characterized by a thick milky, protein-rich fluid, which has a striking odor after bacterial colonization.

Science

Mechanisms of skin graft take

Skin grafting is the transfer of autologous skin cells left in anatomic order but without an intact blood supply. Therefore time and the recipient surrounding conditions limit the vitality. The operative procedure allows for nearly immediate

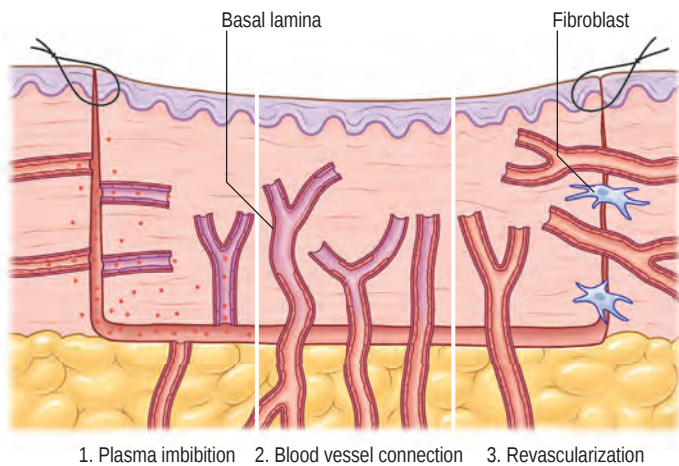


Fig. 15.3 The concept of revascularization of the graft. Skin graft take is characterized by three main phases: (1) Plasma imbibition: the graft is initially nourished by the plasma circulation from the wound side. (2) Blood vessel connection: three different theories of how the skin graft revascularizes on the wound bed are described: (a) graft vessels regress and leave a basal lamina infrastructure followed by ingrowth of host epithelial cell ingrowth; (b) the reconnection of graft and host open ends; and (c) the ingrowth of endothelial cells from the host into the graft. (3) Revascularization of the skin graft. (Adapted from Capla JM, Ceradini DJ, Tepper OM, et al. Skin graft vascularization involves precisely regulated regression and replacement of endothelial cells through both angiogenesis and vasculogenesis. *Plast Reconstr Surg.* 2006;117: 836–844.)

coverage of large wound areas. Meshed grafts allow further expansion of skin but leave multiple small wounds that are re-epithelialized, mainly from the mesh within a few days. Skin can also be expanded through multiple small skin island grafts (as in Reverdin's technique) that stimulate granulation tissue, probably by excreting growth factors. In STSGs, keratinocytes on the basal layer show high proliferation rates, which may ultimately stimulate growth factor excretion.¹⁷

Three phases of skin graft take are commonly described: (1) serum imbibition; (2) revascularization; and (3) maturation (Fig. 15.3).

Serum imbibition

In the first days, before the graft revascularizes, oxygen and nutrients diffusing through the plasma between the graft and the wound bed will nourish the skin graft. Huebscher in 1888¹⁸ and Goldmann in 1894¹⁹ theorized that skin grafts might be nourished by host fluid before vascularization of the graft occurs. They referred to this as "plasmatic circulation."^{18,19} Later, Converse *et al.*²⁰ altered the term to "serum imbibition", as fibrinogen changes into fibrin that fixes the skin graft on to the wound bed in the absence of real plasmatic flow. Converse's studies show that skin grafts gain up to 40% of their initial weight within the first 24 hours after grafting and then this gain is reduced to 5% at 1 week postgrafting.²⁰ In the first hours, passive absorption of serum from the wound bed causes edema, which resolves when the revascularization is functional (see Fig. 15.3).

Revascularization

Revascularization is critical for long-term skin graft survival. Early studies in the 19th century^{21–24} suggested a connection between the wound bed and graft vessels, referred to as

inosculation,^{3,18,19,25} but the mechanism of revascularization remained unclear for many years.

Three hypotheses of revascularization are supported by the literature, each of them probably contributing to the process: anastomosis, neovascularization, and endothelial cell ingrowth. Anastomosis is the process of reconnection between the blood vessels in the recipient site wound bed and the graft.^{21,23,24,26–28} Neovascularization is characterized by new vessel ingrowth from the recipient site into the skin graft. The last mechanism describes endothelial cell proliferation and sliding from the recipient site, utilizing pre-existing vascular basal lamina as a structure, while in the graft endothelial cells gradually degenerate.^{22,24,29–31}

The process of revascularization begins as early as 24–48 hours after grafting.^{32,33} Many authors describe vessel ingrowth mainly from the wound bed and less so from the wound margins, since no significant increase in blood vessels was seen in graft margins after skin grafting.^{21,24,32–35} Studies supporting vessel ingrowth from the host as the main mechanism of skin graft revascularization have been controversial with respect to time course and the mechanism of host-graft vessel interactions.^{23,36} Some early studies demonstrated by intravenous injection with radioisotopes that blood flow in the graft was established 4 days after grafting.³⁷ Similarly, studies using India ink showed graft vessel stain as early as 2 days post-grafting.²³ More recently, it was demonstrated, using a transgenic tie2/pacZ mouse model, that vessel ingrowth appears in the periphery of the graft (following blood vessel regression in the graft) from day 3 until day 21.³⁸ Zarem *et al.*²² suggested that the process of vascularization of full-thickness skin grafts in the mouse is dominated by vascular ingrowth from the recipient using a modified transparent skin chamber. Henry and Friedman³⁶ proposed the theory that endothelial cells of superficial graft vessels degenerate and that host vessels profit from the basement membrane-covered infrastructure for new vessel ingrowth. In 1967, other investigators confirmed this theory using the graft hamster cheek pouch and showed a similar vessel pattern before and after grafting.³⁹ Converse and Ballantyne further investigated endothelial cell ingrowth into the graft using diaphorase, a marker of viable vascular endothelium. They found increased diaphorase levels in the graft bed 4 days after grafting, supporting the theory of vascular ingrowth from the host. As very few functional anastomoses were present, the authors concluded that both mechanisms, inosculation and vascular ingrowth, were important in the process of revascularization.³¹ Vessel regression was also supported by NADH diaphorase activity loss during the first 4 days after grafting that was probably taken up by new vessel ingrowth.^{29,38,39} The conclusion that endothelial cells utilize preformed tunnels of basal lamina was triggered by the observation that initially empty graft vessels subsequently became infiltrated with leukocytes and that ingrowing vessels used the white blood cell-filled channel as a conduit.²² Later studies showed a central refilling of the graft vasculature as early as 48 hours, leading to the conclusion that early anastomosis between host and graft vessels may play a major role in graft revascularization, as vessel growth occurs at about 5 $\mu\text{m}/\text{hour}$ and angiogenesis would take at least 5 days to reach the 600- μm -thick murine dermis.^{22,40} In 1987 Demarchez *et al.*⁴¹ supported this hypothesis by grafting athymic mice with human STSGs. Double labeling of cross-reacting antifactor VIII and a human-specific

antitype IV collagen antibody showed initial anastomosis between graft and host vessels. Murine host cells gradually replaced vascular structure and the extracellular matrix of the skin graft. Later studies confirmed this hypothesis by observing a similar blood vessel network of the skin graft at the donor site and after revascularization of the graft between 96 and 120 hours after grafting.³²

Capla *et al.* further showed that about 20% of blood vessels supporting the microcirculation on day 7 after grafting occurred by bone marrow-derived endothelial progenitor cell-derived vasculogenesis.³⁸ Recent studies measured increased levels of growth factors related to hypoxia-induced angiogenesis (hypoxia-inducible factor-1 and vascular endothelial growth factor) 24–240 hours after grafting, a process that may also contribute to host vessel ingrowth (see Fig. 15.3).³²

Maturation

Once the skin graft is completely integrated, the same graft and surrounding tissues remodel and contract, similar to the last phase of wound healing after re-epithelialization is complete. Skin grafts take at least 1 year to complete maturation, with the extension of this process continuing for several years in burn victims and children. Scars from skin grafts can continue to improve for a number of years, often making prolonged conservative therapy worth considering.

Skin graft vascularization contributes to prevent underlying tissue contraction. Fibroblasts from surrounding tissues and from blood circulation become activated and repopulate the wound at the interface between the graft and the recipient site. As collagen is deposited, cross-linking allows the extracellular matrix to resist mechanical insults. Fibroblasts develop fibers called alpha-smooth-muscle actin (alpha-SMA) that exert contractile forces on the extracellular matrix. The development of alpha-SMA coincides with the differentiation of fibroblasts into myofibroblasts and wound contraction. During wound maturation, the epithelium from the edges of the wound produces a basal lamina on the open surface while sliding across and progressively covering the immature granulation tissue.

During the remodeling phase, all immature blood vessels necessary to support the initial phases regress and eventually disappear. The remodeling phase of wound healing is the longest, lasting from several months up to years.

Skin appendages and functional structures

Hair follicles, sweat glands, and dermal nerves can often be transferred within thick STSGs and full-thickness skin grafts (see Fig. 15.2). Thin STSGs will not allow the transfer of hair or other adnexal glands, as the regenerating bulb is not harvested. Hair regrowth can occur in STSGs but, due to the shallow depth of harvest, is rather unlikely. Full-thickness and composite grafts will show hair regrowth 2–3 months after grafting.

It is still unclear how nerves regrow into the skin graft. Studies demonstrated that recipient nerves use the basal lamina infrastructure of degenerated blood vessels and Schwann cells of donor nerves to grow. Although histological images reveal similar neural structures between healthy skin and integrated skin grafts, patients report abnormal sensation, including hypersensitivity and pain, up to 1 year after grafting. Usually patients regain sensitivity of the grafted area after 1 year, but the result is not completely normal.

Neural reconnection to sweat glands will reactivate their function up to 3 months after grafting. For this reason, moisturizing of the skin graft is advised for at least 3 months to avoid dryness.

Full-thickness skin grafts include skin appendages that can survive and be functional at the recipient side, while STSGs do not contain the deep structure skin appendages and remain without glandular function or hair growth.

Clinical application

Skin wounds that extend into the deep dermis heal through the mechanisms of scarring and wound contraction. For large

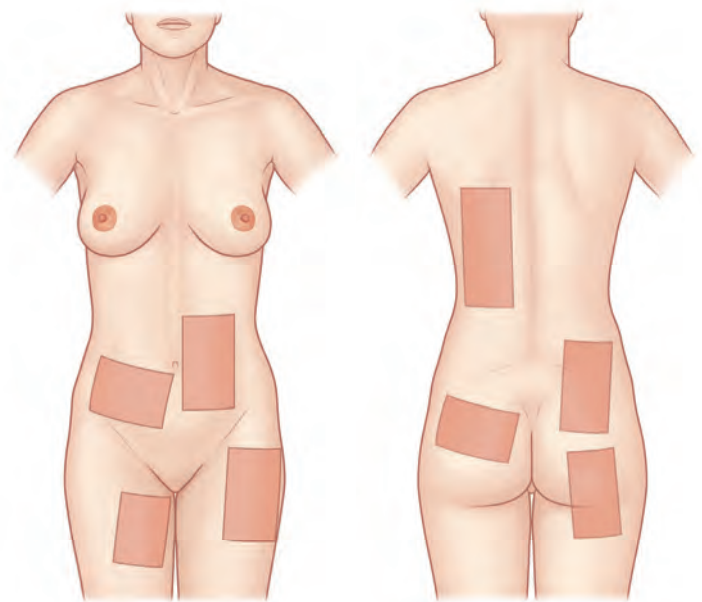


Fig. 15.4 Split-thickness donor sites. Split-thickness donor sites are commonly chosen from the anterior thigh or abdomen. Color-matched and aesthetically less evident areas can only be chosen if healthy skin is available. In burn patients with only limited availability of nonaffected skin, skin will be taken from any part of the body. Face and hands are preferentially spared from skin harvest. (Adapted from Knipper P. *Mission: plastic surgery under challenging conditions*. Maitrice Orthopédique. 2002:118 and 2003:112.)

Table 15.1 Definition of origin of the skin graft

Graft type	Graft origin: donor and recipient
Autograft	Same subject
Homograft	Same species
Isograft	Different subject Same genetic background
Allograft	Different subjects Same species
Hetero- or xenograft	Different subjects Different species

(Adapted from Andreassi A, Bilenchi B, Biagioli M, et al. Classification and pathophysiology of skin grafts. *Clin Dermatol*. 2005;23.)

Table 15.2 Indications, advantages, and disadvantages of thin split-thickness skin graft (STSG), thick STSG, and full-thickness skin graft (FTSG)

	Indications	Advantages	Disadvantages
Thin STSG	Debrided burn wounds Chronic wounds with less vascularized wound beds Exposed flap areas Acute well-vascularized wounds	Fast donor site re-epithelialization Multiple possibilities to reharvest the same area Good graft take	Contraction of the skin graft Graft quality limited because of minimal dermal thickness
Thick STSG	Same indications as thin STSG	Less secondary graft contraction compared to thin STSG Graft more stable because of thicker dermal layer Good graft take	Slower donor site re-epithelialization
FTSG	Reconstruction of functional areas such as in the face or hand Noninfected, well-vascularized wound beds	Minimal to no secondary graft contraction Excellent skin quality, stability Hair regrowth and skin appendage function	Limited availability Nontake risk is higher in a less vascularized wound bed

wounds this process leaves the body at risk of infection and when it occurs around joints, this can lead to significant scar contractures that affect functionality. For example, in anterior neck wounds, the contractile processes can be so strong that, over time, the chin can be fixed to the chest, often with a thick scar. Also, wounds that are left open for months to years can degenerate into skin cancer (Marjolin's ulcer). For these reasons, methods that rapidly facilitate wound coverage or resurfacing are desired.

Skin grafting is still the gold standard to cover large areas of skin loss. The concept is to take skin from an area where

the donor site will heal with minimal scarring and transplant it to an area of need. As skin grafting always leaves some sort of scar, donor site considerations are important when balancing the needs of the recipient site for a given skin graft.

Skin grafts can be of different origin (Table 15.1), from different anatomical sites (Fig. 15.4), and can be harvested in different thicknesses (Table 15.2). Depending on the histological level of the graft the skin graft type is classified by thin and thick STSGs, full-thickness skin grafts, and composite grafts (see Fig. 15.2). Skin grafts are further classified according to their thickness into thin (0.15–0.3 mm, Thiersch–Ollier), intermediate (0.3–0.45 mm, Blair–Brown), and thick (0.45–0.6 mm, Padgett). Skin grafts thicker than 0.6 mm usually correspond to full-thickness skin grafts and are called Wolfe–Krause grafts.^{42–44}

Split-thickness skin graft

The thickness of the dermal layer classifies the STSG as either thin or thick. An STSG consists of epidermis and a variable amount of superficial to profound (papillary) dermis. As the dermis is responsible for the viscoelastic property of the skin, it is crucial for stability of the future skin. The amount of dermis grafted is key to the outcome: body areas with high mechanical friction are ideally grafted with thicker dermal layers. If donor sites do not allow this, skin quality can be improved with a combination of skin and dermal substitute grafts.

Thin STSGs include the epidermis and a thin layer of the dermis (see Fig. 15.2). STSGs are commonly taken from the lateral thighs and trunk (see Fig. 15.4). They do not include the full length of appendages and are therefore unlikely to grow hair or to develop full sweat gland function. The main advantage of thin STSGs is the reduced morbidity of the donor site and the possibility of performing multiple harvests from the same donor area about 2 weeks after the previous harvest. Although thinner grafts allow for more frequent reharvest, they result in additional wound contraction. The clinician must weigh the advantages and disadvantages of these conflicting goals when deciding the thickness of the graft.

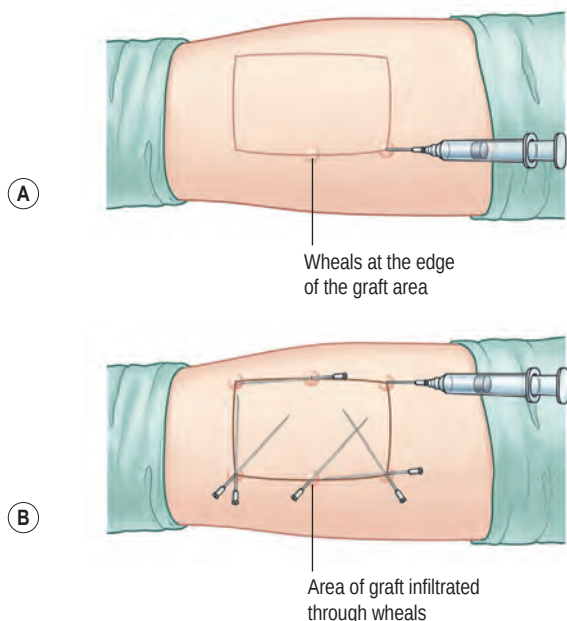


Fig. 15.5 Donor site preparation. Bleeding is one of the most important complications of excision and grafting. To reduce the severity of bleeding during excision, the fatty tissue under the graft can be infiltrated with a solution of epinephrine diluted in saline ("tumescent technique"). (Modified from King M, Bewes P. *Skin grafts and flaps: the general method for split skin grafting*. In: *Primary Surgery*, Vol. 2. Trauma. Oxford: Oxford University Press; 2009. By permission of Oxford University Press Inc.)

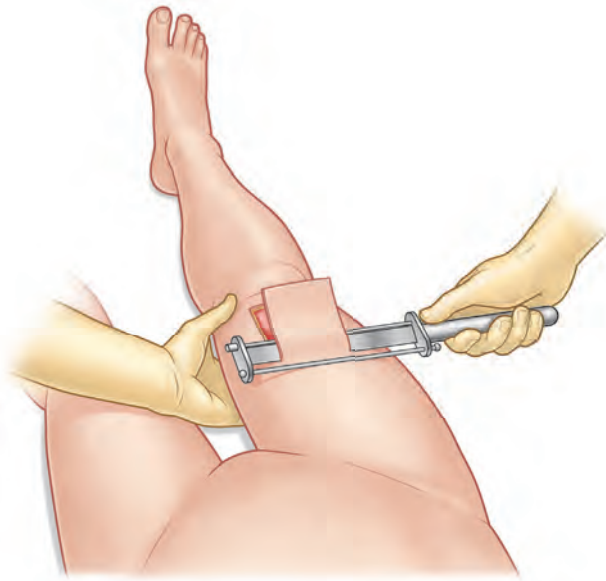


Fig. 15.6 Split-thickness harvest with a manual knife. Alternatively, if no electrically driven dermatome is available, skin grafts can be carefully harvested with a manual knife. This procedure requires experience and harvest of even thickness is difficult. (Adapted from Knipper P. *Mission: plastic surgery under challenging conditions*. Maitrise Orthopédique. 2002:118 and 2003:112.)

Thick STSGs include more dermis with a greater number of full hair follicles and glandular structures (see Fig. 15.2). These grafts will likely develop some hair growth and sweat gland function about 2–3 months after grafting. Thick STSGs are commonly selected to cover areas of high mechanical friction, such as joints, plantar soles, and the palm. Since hair regrowth is common in thick STSGs, the donor site should be carefully chosen to avoid unpleasant hair growth. The sensitivity and function of sweat glands are often better in thick than in thin STSGs. Because of decreased nutrient diffusion, thick grafts require a better recipient wound than thin grafts during the revascularization process. Therefore, thick grafts should be avoided in unhealthy wound beds such as in chronic ulcers. The donor site usually heals with more obvious scarring and discoloration but less graft contraction.

Technique

To reduce bleeding during skin harvest some surgeons prefer to infiltrate the donor site area primarily with epinephrine diluted in saline subcutaneously (tumescent technique: Fig. 15.5). If small to medium-sized areas of skin are needed and a dermatome is not available, surgeons can skillfully take skin grafts with a surgical knife or with the oscillating Goulian knife (Fig. 15.6). The disadvantage of skin grafts taken manually is the difficulty of achieving uniform depth that can result in aesthetically unpleasant donor and recipient site skin pattern. To increase the uniformity and expedite the harvest of skin grafts, a number of electrical or air-powered dermatomes have been designed to take uniform small to large skin grafts. Powered dermatomes have adjustable guards to set the graft thickness. There is a fair amount of variability in thickness depending on how hard the operator pushes on the dermatome. Drum dermatomes are precision instruments that can take large graft areas reliably (Fig. 15.7). They require

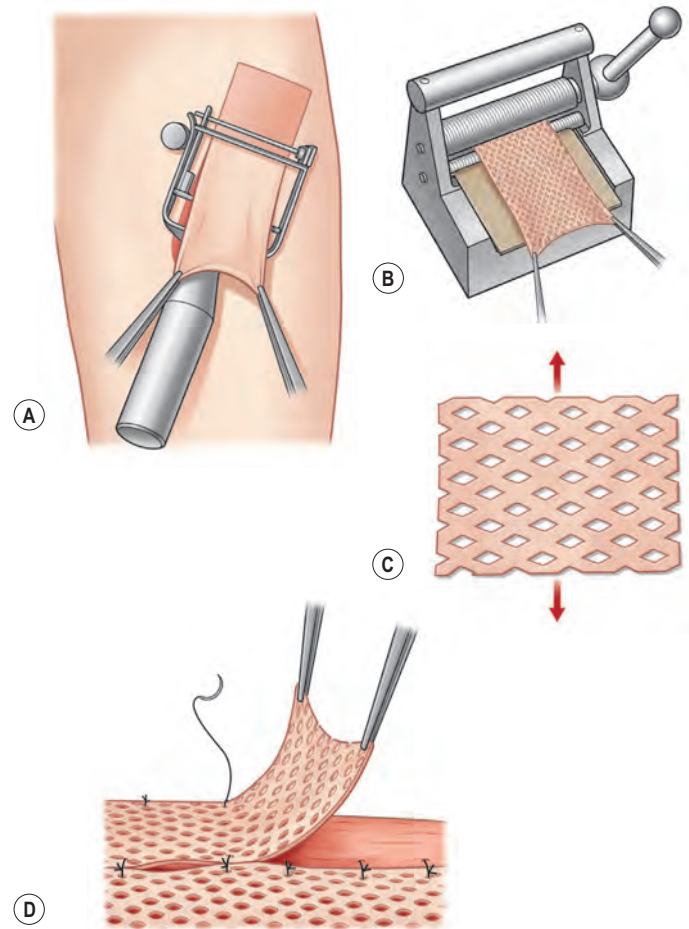


Fig. 15.7 Split-thickness harvest and grafting. (A) Split-thickness skin graft (STSG) harvest with an electrically driven dermatome at the anterior thigh. (B) The skin graft should be positioned flat on the mesh template: this can be performed by multiple slits to (C) expand the graft up to six times its original size. (D) Meshed STSGs are ideal to cover large and uneven wounds. Stapler fixation is a time-saving method to fix large grafts. (Adapted from Orgill DP. *Excision and skin grafting of thermal burns*. N Engl J Med. 2009;360:893–901.)

placement of adhesive on the skin and an oscillatory movement by the operator.

When possible, harvesting the skin graft first and covering the donor site will avoid contamination from the wound. When the excisional preparation of the recipient site needs to be performed first, a separate instrument set-up for the donor site can be considered. The size of the graft needed should be accurately measured prior to harvest. The graft thickness can be adjusted by a lever near the end of the dermatome between 0.1 and 1.0 mm. The surgeon presses the dermatome at 45° to the skin surface on to the tissue and moves the device from distal to proximal with uniform pressure and speed (see Fig. 15.7). A second assistant can pick up the skin graft with two anatomical forceps during the harvest process to avoid damage of the graft. If the desired length is taken, the dermatome will cut the edge when elevating it while running the motor. Keeping the graft moist with saline-impregnated gauze is of vital importance if not immediately grafted.

Larger skin grafts should be incised with an 11 knife multiple times to allow wound fluid drainage and prevent collections between the skin graft and the wound bed.

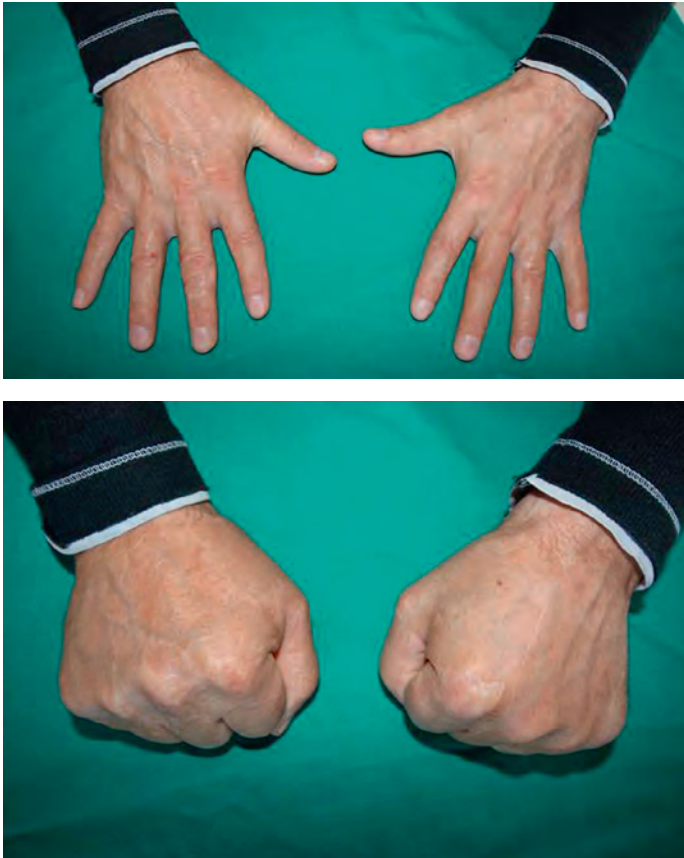


Fig. 15.8 Non-meshed split-thickness skin graft coverage 18 months after debridement of 2nd deep burn injury of the hands. Note excellent aesthetic and functional results.

Meshed skin graft

STSGs can be enlarged up to six times their original size. Enlargement of the graft can vary from just a few manually applied perforations with an 11 blade to a systematic enlargement with a hand-powered meshing device (mesher) that applies multiple slits at regular intervals (see Fig. 15.7). Meshed grafts are often used following large burns when the wound area exceeds available healthy donor sites. Meshed skin grafts are also very helpful to cover irregular geometric surfaces, such as around joints, as they minimize folds in the graft. Development of contractures should be taken into consideration in functional areas. If meshing is not necessary or should be avoided in important aesthetic or functional areas, such as face, neck and hands, the graft should be perforated multiple times to allow fluid removal under the graft (pie-crusting) that can minimize the risk of hematoma, seroma, or infection under the graft. Unmeshed STSG can achieve excellent aesthetic and functional results (Fig. 15.8). Using different mesh templates, from 1:1 to 1:9, can regulate the extent of the enlargement of meshed grafts. The most commonly used mesh ratio is 1:1.5 in smaller wounds, while a mesh ratio of 1:3 and 1:6 is often needed to cover large burns.

Meshing devices are manual and come with different plastic templates where the skin graft is placed on upside down. The graft should be taken with anatomical forceps to avoid mechanical damage. The mesh gaps will be subsequently filled by keratinocytes from the skin stripes

(Fig. 15.9). This process takes longer with higher mesh expansion ratios. Since grafted cells excrete growth factors, underlying granulation tissue will be stimulated until full re-epithelialization occurs. Aesthetically unpleasant hypergranulation in the open areas of the mesh are therefore more often seen in large mesh ratios often leading to an uneven cobblestone-like skin relief (Fig. 15.10). Meshed skin grafts leave unsightly long-term results that need to be considered when selecting this technique. Very thin meshed skin grafts used in combination with dermal substitutes or keratinocyte cultures are other strategies to mitigate the result (see Fig. 15.8).

Full-thickness skin graft

Full-thickness skin and composite grafts are limited in availability but show excellent function and sensitivity after engraftment. Full-thickness grafts should be considered in the

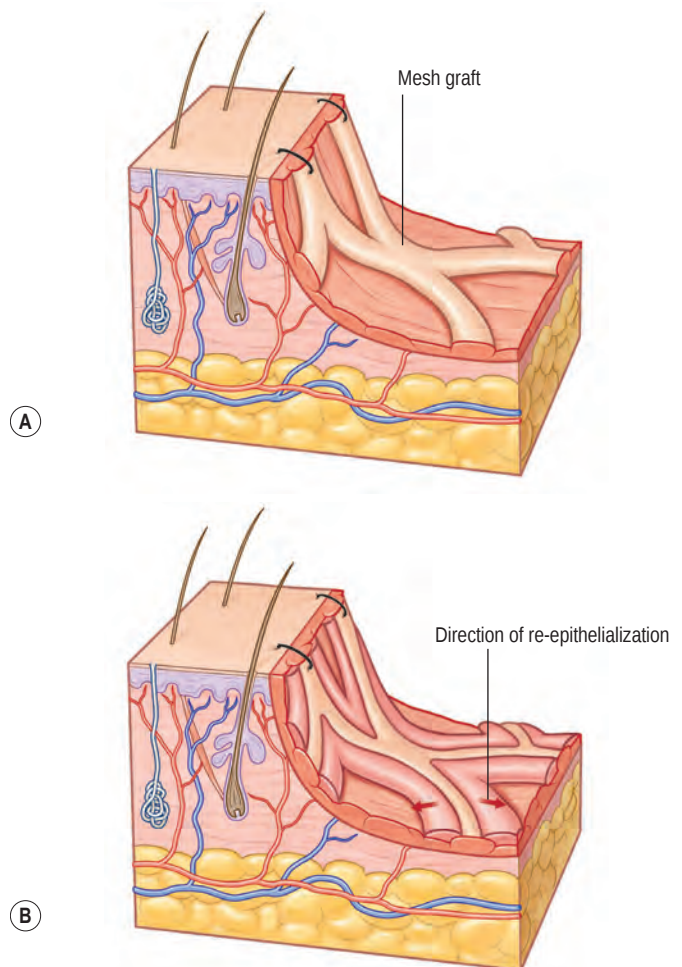


Fig. 15.9 Meshed split-thickness skin graft (STSG) and re-epithelialization. The pattern of the meshed STSG is evident even after completely healed skin and is more evident with the enlargement ratio used. Therefore, surgeons possibly prefer to expand with 1:1.5–1:2 ratios as maximum. (A) The meshed skin graft can be fixed with staples or sutures. (B) Open surfaces will be gradually re-epithelialized from the skin stripes. In largely expanded grafts the stimulation of the wound bed from the engrafting cells leads to hypergranulation, resulting in an unpleasant aesthetic pattern. (Adapted from Orgill DP. *Excision and skin grafting of thermal burns*. N Engl J Med. 2009;360:893–901.)



Fig. 15.10 Uneven skin relief, “cobblestone” pattern in a left forearm 3 years after deep burn injury, debridement and coverage by a 1:3 ratio meshed split-thickness skin graft.

reconstruction of aesthetically dominant (face) or functionally important (hand) areas. Full-thickness grafts from the retroauricular region and above the eyebrows are an excellent choice to maintain tissue quality and color of the surrounding skin in the face (Fig. 15.11). If needed, foreskin can also be used and in adults retroauricular skin is helpful in face reconstruction. Also, excess skin from the upper eyelid and submental area can be taken into consideration for full-thickness

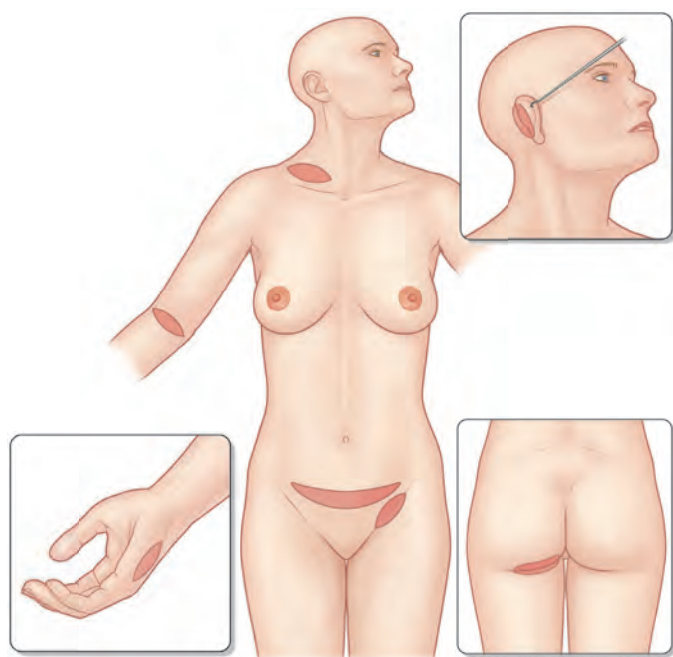


Fig. 15.11 Full-thickness donor sites. Full-thickness skin graft (FTSG) donor sites are limited and require primary wound closure or split-thickness skin grafting after harvest. FTSG are indicated in the reconstruction of smaller lesions in aesthetic (face) or functional areas (hand). Larger FTSG can be taken from the buttock fold and the infra-abdominal fold. Ideal for reconstruction of the hand is the hypothenar area and the anterior wrist fold. The main axis of the elliptically shaped hypothenar graft should be positioned slightly dorsal to the glabrous–skin border to avoid a hypersensitive scar. For face reconstruction, FTSGs are taken from the retroauricular or, often used in children, the superior eyebrow regions for optimal color match. The inguinal fold is frequently used because of good aesthetic outcome at the donor site. Other areas are the subclavicular, the infra-abdominal, and the elbow fold as well as the inner upper arm. (Adapted from Knipper P. *Mission: plastic surgery under challenging conditions*. Maîtrise Orthopédique. 2002:118 and 2003:112.)

reconstruction if the patient is comfortable with an aesthetic-like intervention.

In hand reconstruction, elbow crease and wrist fold grafts have been described but should be avoided in cultures where these donor site scars may result in stigmatization of the patient as they can be associated with suicide. Hypothenar skin is useful for glabrous reconstruction but can leave a painful scar that can cause an unpleasant sensation if the hand is positioned on a table in a relaxed position. Therefore, full-thickness skin graft from the hypothenar area should be harvested elliptical with the main axis and slightly more dorsal in relation to the glabrous–skin border (see Fig. 15.11).

Full-thickness skin grafts are taken in an area where loose surrounding skin is available to achieve primary closure. Skin grafts can be designed elliptical and excised with a knife. Harvesting should be carried out trying not to elevate the underlying tissue. Most of the full-thickness grafts need defatting and this can be easily performed by spreading the graft over the index finger and trimming the fat tissue tangentially to the skin. Defatting of the graft will encourage graft take (Fig. 15.12).

Composite graft

Composite grafts include a layer of subcutaneous fat tissue under the dermal and epidermal layer. The donor sites are principally the same as the full-thickness donor sites. Since fat tissue is less vascularized and more vulnerable to ischemia, optimal revascularization is needed in order to achieve graft survival. Composite grafts can be used in children as they show a remarkable capacity to revascularize thicker grafts. Some surgeons use composite grafts to reconstruct the nasal tip, the alar, and the columella in cleft lip patients.⁴⁵

Over time, the appearance of skin grafts tends to improve in both color and texture. Nevertheless, skin grafts rarely have the aesthetic appearance of normal skin and patients should be advised about the likely final appearance of the graft.

Skin fixation and dressing

Once the autologous skin is grafted on to the wound site the revascularization depends on multiple factors. One of the most important factors to achieve stable taking is the immobility of the graft during the revascularization process. An open technique requires labor-intensive monitoring on the graft and any fluid that is formed beneath the graft is rolled out with a cotton-tipped applicator. More often, skin grafts are fixed through a series of sutures and overlying compressive dressing materials (bolster: Fig. 15.13). Scattered sutures through the graft on to the wound bed can additionally immobilize larger skin grafts. If large and multiple skin grafts are placed, as frequently needed in burn victims, fixation can be performed with staplers to shorten operation time. Staples are painful when removed and may be overgrown by skin, especially in large skin grafts. Vacuum-assisted pressure devices can be used with a protective interface of petroleum gauze or a silicone sheet to permit continuous compression on to the graft and fluid removal. The suction dressing is especially useful if fast mobilization is desired in patients with wounds in joint regions or the lower extremities (see Fig. 15.13). Compression to stabilize the graft on to the wound bed should be performed until 5–10 days after grafting, when the graft is usually stable and wound areas are completely closed.

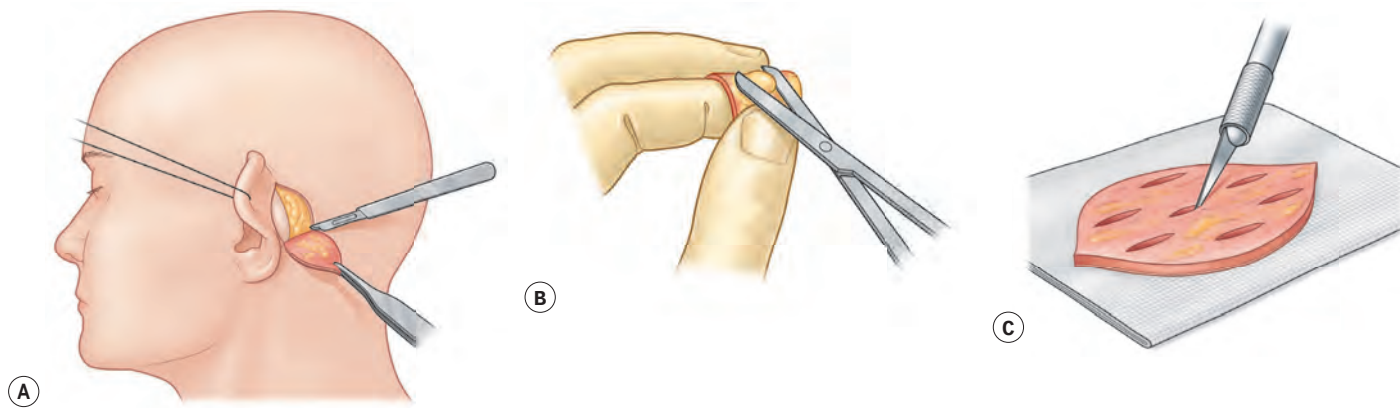


Fig. 15.12 Full-thickness skin graft (FTSG) harvest and preparation. FTSGs should be designed elliptically to achieve primary wound closure without deforming surrounding tissues. This fact is usually given if a length:width ratio of 1:3 is followed. **(A)** After sharp excision of the graft the surgeon should elevate the graft if possible without fat tissue and protect the graft by handling it with a skin hook or anatomical forceps. **(B)** Defatting is an important process to avoid fat necrosis after grafting and to facilitate direct revascularization of the wound bed. The graft can be easily defatted with scissors by stretching the graft upside down over the index finger. **(C)** To allow fluid exit from the wound bed, FTSG should be incised with a sharp knife in multiple sites. (Adapted from Knipper P. *Mission: plastic surgery under challenging conditions*. Maîtrise Orthopédique. 2002:118 and 2003:112.)

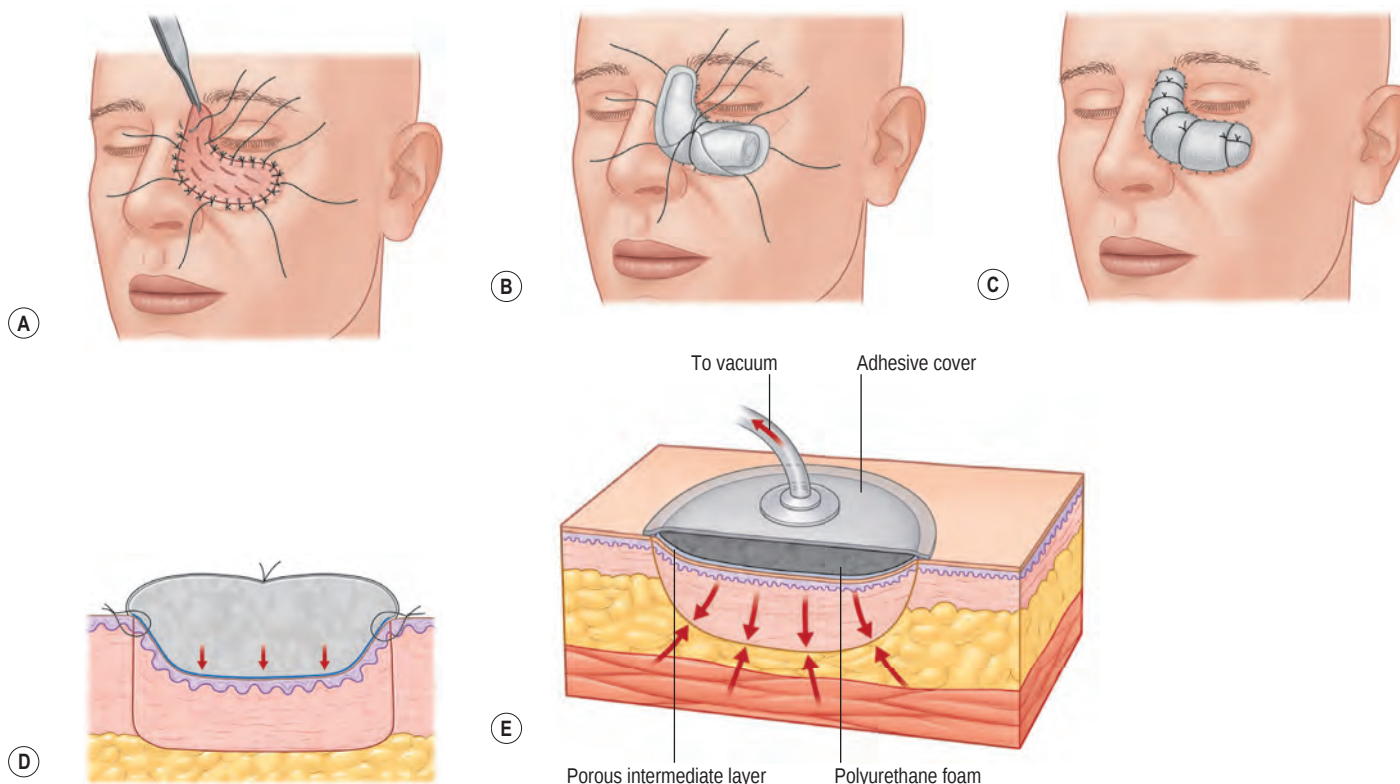


Fig. 15.13 Fixation of a skin graft. Skin grafts require precise contact with the wound surface, and fluid collections and micromovements are to be avoided. A bolster dressing is an excellent method to press and stabilize smaller skin grafts on to the wound, particularly in the face or hand areas. **(A)** The graft is placed and sutured on to the wound and sutures are left intentionally long. **(B)** A first layer of nonadhesive fat dressing is placed on the graft and covered with a bolster of cotton or gauze that is sutured face to face over the second layer. **(C)** The second layer will exert mild pressure on to the graft that stabilizes the graft and allows fluid exit into the bolster dressing. **(D)** The bolster dressing will precisely adapt the skin graft on to the wound bed to optimize the conditions for the revascularization process. **(E)** Vacuum-assisted closure dressing to fix skin grafts: the fixation of the skin graft is an elegant method, especially if larger and uneven areas that cover joints are grafted. Continuous suction and compression on to the wound bed ensure fluid removal and stabilization of the graft. The skin graft will be fixated as usual and the first dressing should be either a nonadhesive perforated silicone dressing or a petroleum gauze to avoid maceration of the graft by the open polyurethane foam. Some surgeons use the moist white foam without interface to fix the graft. (A, C Adapted from Knipper P. *Mission: plastic surgery under challenging conditions*. Maîtrise Orthopédique. 2002:118 and 2003:112. B, Adapted from Chase RA. *Atlas of Hand Surgery*. Philadelphia: WB Saunders; 1974.)

Splints can be used as adjuncts if the risk of wound contraction is high, such as in chin scar release or in joint and web space release of the hand. These splints or casts should be worn up to several months after grafting, in the beginning 24 hours per day, later during the night, to avoid the loss of mobility. Physiotherapy and scar massage are also important elements for obtaining better results with skin grafts.

Negative-pressure wound-healing devices also make very effective bolsters, especially on large grafted surfaces and chronic ulcers.^{46–48}

Sealants

Fibrin glue can also be helpful to assist skin graft fixation. In this case, some surgeons spray fibrin glue on to the skin graft dermis just before placing it on to the wound site. The fibrin network may even act as a provisory extracellular matrix under the graft.⁴⁹

First dressing change

The first dressing change should occur once the skin graft is revascularized and has a stable physical connection to the wound bed. Early dressing change around the third day after grafting may allow for predicting the “take rate” of the graft but risks secondary graft loss through shear forces that disturb nascent vessel connections. More commonly the dressings are taken off for the first time 5–10 days after grafting.

Recipient site considerations

Before planning a skin graft, several factors have to be taken into consideration to achieve optimal tissue cover at the wound site. The wound bed quality has to be optimized for a successful “take” of the graft and the skin color, thickness, and mechanical resistance of the donor site area should ideally match the recipient site skin quality. Wound conditions often found in chronic or insufficiently debrided burn wounds and characterized by low wound bed vascularization or high bacterial loads will not allow skin grafts to be taken.

Wound bed preparation

The successful engraftment of skin grafts highly depends on the quality of the wound bed. Revascularization particularly depends on a vital recipient wound bed. A good quantity of blood vessels near the surface is critical in order to support graft viability. Irradiated, ischemic and scar tissue, bone, and tendon do not ordinarily have sufficient blood supply to allow the skin graft to take. If highly vascularized peritendon and periosteum are still intact, skin grafts can be performed. In chronic wounds re-epithelialization occurs at the wound margins that can grow into the tissue and may inhibit the lateral reconnections of the graft. Therefore, wound margins should be sharply excised with a blade before grafting.

Experimental data suggest that the bacterial level must be brought down below the critical level of 10^5 bacteria per gram of tissue to allow a skin graft to take. The practical problem with quantitative bacterial cultures is that it takes about 48 hours to obtain the result, long after the decision to graft is typically made. As a result, this methodology seems most commonly applied to research studies. Surgeons often take a fairly aggressive approach to making sure all necrotic tissue

has been debrided and that the wound is clinically “clean” prior to grafting.

Wound debris or necrotic tissue physically inhibits and chemically slows ingrowth of blood vessels into the skin graft. Wounds that were left open for several days contain high bacterial loads and therefore need to be extensively debrided before skin grafting. Preparation of the recipient site commonly occurs by sharp excision, but can also be performed using a variety of other debridement techniques, including laser, water jet, and ultrasound as well as standard dressing changes. Surgeons have learned over time that a “granulating” wound has a high likelihood of taking a skin graft. Active bleeding of the wound bed will likely lead to blood collection between the graft and the wound bed, inhibiting graft take. Accurate hemostasis can be performed with bipolar cautery and larger blood vessels can be ligated with fine resorbable sutures.

If tendons or bones are exposed without peritendon or periosteum, the surrounding soft tissue can often be adapted to cover critical structures before skin grafting. Small areas of tendons and bones can either be prepared by vacuum-assisted closure therapy to grow granulation tissue from the sides or dermal substitutes can be used to cover functional structures.

Functional consideration

Skin grafts can often provide functional and aesthetic skin reconstruction. Consideration needs to be given to the size of graft needed, the degree of wound contraction expected, the color and texture of the skin required, and the need for adnexal glands. The amount of wound contraction expected is inversely related to the amount of dermis in the skin graft.

Full-thickness grafts, those that take the entire epidermis and dermis, maximally restrain contractile forces and give excellent cosmetic results. Full-thickness skin grafts are frequently used for nipple-areola reconstruction, syndactyly release, or ectropion release. Full-thickness grafts are in short supply and can be augmented by tissue expansion prior to harvesting full-thickness skin grafts.

Very thin grafts such as epidermal grafts result in a donor site that heals quickly with minimal contraction but provide little constraint to wound contraction. The surgeon can use this as an advantage if wound contraction is desired. For example, on large scalp wounds or abdominal wounds, wound contraction may be desired to keep the skin graft as small as possible while pulling the wound edges together over time. Secondary excision of the contracted skin graft and primary wound closure can be performed in a second stage to achieve best functional and aesthetic results.

As the skin thickness varies throughout the body, a variety of skin thicknesses are available for use. For example, full-thickness upper eyelid skin is very thin but provides good resistance to wound contraction. Thicker skin is available in the trunk and leg region, where thick STSGs can be taken, leaving enough adnexal structures and dermal thickness to minimize donor site scarring.

Aesthetic considerations

Skin color is determined by a complicated integration of skin texture, melanin pigmentation, and blood flow. In general,

replacement of tissue from a similar or adjacent site will give the best color match. In the face, this is often the most critical aesthetic area and choosing donor sites such as supraclavicular, posterior auricular, upper eyelid or scalp skin grafts can often lead to an excellent color match. For darker areas of the skin, such as the nipple–areola complex, grafts from the contralateral areola or genitalia have been used. More commonly today, skin grafts in this area can be tattooed with vegetable dyes to give an excellent color match.

Skin texture is most commonly an issue when dealing with glabrous skin (palms and soles of feet). In this case, placing a nonglabrous skin graft to cover these areas can result in a very unnatural look, often with significant color match differences. Glabrous skin grafts are obviously in short supply but can be harvested from the hypothenar eminence. Skin adnexal glands are difficult to replace but can sometimes be successfully transferred with full-thickness grafts.

Donor site considerations

The obligatory scarring or discoloration associated with donor sites must be considered when taking a skin graft (Fig. 15.14). For large surface area burns, the surgeon must use whatever donor site is available to close the wound; in contrast, for smaller grafts, a thorough discussion of the donor site possibilities with the potential risks and benefits allows for the best skin match with the least iatrogenic damages.

Common donor sites include the thigh, trunk, and buttocks, regions frequently covered by clothing (see Fig. 15.4).

When defects of the face need to be covered, full-thickness skin grafts are often preferred. The donor area for a graft on the face should be preferably chosen from among the scalp, neck, and supraclavicular area to obtain the best color match. Important aspects are the thickness, color, and texture of the graft, which should closely match those of the recipient site.

Eyelid skin, which is thin with a few glandular structures, is generally best replaced by eyelid skin. Thick, highly glandular nasal skin can be replaced by skin from the nasolabial folds, supraclavicular area, or anterior auricular area.

In trauma, avulsed (degloved) skin can often be prepared by extensive defatting and regrafted primarily⁵⁰ or stored and used later.



Fig. 15.14 Donor site three years after split-thickness skin graft taken with a dermatome at the forearm. Note slight hypopigmentation.

Full-thickness donor sites in the head and neck are pre- and postauricular regions (the first is generally thicker), nasolabial crease, supraclavicular region, eyelids, and neck.

Other common regions include the inguinal crease, which is often used to cover large defects. In this case it is important to harvest laterally and away from potentially hair-bearing regions of the pubis. This area generally heals well and is hidden (see Fig. 15.11).

In nipple–areola reconstruction after mastectomy, a full-thickness graft from the contralateral region is often taken in combination with a full-thickness graft from the groin.

Donor sites from full-thickness skin grafts are generally closed primarily. Particular attention should be taken when supraclavicular donor sites are used, as this region is prone to develop hypertrophic scars. Sometimes large donor sites that cannot heal primarily are used for covering extensive defects, for example, in the face or joints. In this case, an STSG can be used to cover the donor site.

Donor site dressing

Topical gauze soaked with diluted epinephrine solution is useful to stop bleeding at the donor site and can be left until the operation is ended, adding an analgesic effect. The donor site of an STSG generally heals (re-epithelializes) in 7–21 days depending on the size and depth of the graft taken and the age of the patient. A myriad of donor site dressings are available with multiple studies on a variety of products. Traditionally, fine-meshed gauze, often impregnated with a petroleum-based product, is placed over the wound and fixed in place. Cotton gauze is placed over this and removed a day or two after the operation. The wound heals under this dressing and the dressing spontaneously comes off when healed. The advantages of this type of dressing system are its simplicity, low cost, and minimal wound care requirement. The work of Winter in the early 1960s⁵¹ showed that a moist wound heals faster. As a consequence many have advocated a simple semioclusive, adhesive, semipermeable polyurethane dressing, although it promotes serum accumulation between the wound and the dressing that should be evacuated by a drain or a syringe. This process can be labor-intensive for a busy inpatient service or difficult to manage on an outpatient basis. In addition, when an infection develops, it can rapidly spread to the entire donor site area with this dressing.

A large number of other dressings, including silver-based, absorptive, and biological, have been studied. In most of the cases the donor site heals spontaneously, thus simple impregnated gauze is still the gold standard. When some complications occur, the harvest site can deepen and become a full-thickness defect, mainly due to infections in the elderly, infants, or critically ill patients. As a consequence, excision and grafting of the donor site may be required.

Skin graft storage

Skin grafts can be stored on a moist gauze at 4°C for up to 2 weeks, although the viability decreases over time. Experimentally, storage can be extended using cell culture media. For degloving injuries, the skin can be defatted acutely and reapplied as a full-thickness graft.

Complications

Hematoma

Any liquid between the wound and skin graft can impair skin graft take. Bleeding represents one of the most important complications after excision and grafting, with up to 100–200 mL of blood for every 1% of body surface area that is excised, particularly from the scalp.⁵² The surgeon must be certain that bleeding has stopped prior to dressing the wound. Suture ligation or cautery can be used to control larger bleeding vessels; oozing can be controlled with pressure and/or pharmacological methods such as topical thrombin, epinephrine, or fibrin glue. To reduce bleeding during excision the area can be primarily injected with epinephrine diluted in saline (tumescent technique: see Fig. 15.5).⁵³ As discussed above, incisions of the graft should be done to allow fluid evacuation through a compressive or suction dressing.

Seroma

Serum imbibition is essential for early skin graft survival. Excessive serum, such as a seroma, will prevent or delay skin graft take. Seromas are better tolerated than hematomas, and adequate fenestrations (pie crusting) can prevent this problem.

Infection

When skin graft infections occur, pus often accumulates beneath the skin graft and can rapidly spread. If an infection is found early, prompt incision and drainage of the fluid beneath the graft can often salvage some or all of the skin graft. A large number of dressings have been developed that carry a variety of topical antimicrobial agents. Silver nitrate, mafenide acetate, and silver ion dressings are commonly used. Bacteria seem not to develop resistance easily to silver products, making these products desirable.

A contaminated wound will not heal and will reject a graft. Some microorganisms, such as *Pseudomonas* spp., can contaminate the wound and cause nonpurulent infections. Even systemic or nonskin-localized infections have been proven to delay or prevent skin graft taking.

Nontake

Unfavorable conditions such as malnutrition, vasculitis, malignant diseases, steroids, and chemotherapeutic medications have all been shown to cause or accelerate nontake of the graft.

Wound contraction

Wounds covered with skin grafts can still undergo wound contraction leading to a scar contracture. After the acute inflammation phase the contraction starts. Fibroblasts from surrounding tissues and from blood circulation start to be activated and repopulate the wound between the graft and the wound bed. Cells at the interface need to build new collagen-rich tissue to replace fibrin and anchor the graft to the wound bed. While fibrin is crucial for early cell migration in the wound bed, collagen deposition allows wound maturation. As collagen is deposited, cross-linking occurs so that the

extracellular matrix becomes mechanically resistant. This increase in mechanical resistance allows mechanical interaction with fibroblasts that develop fibers called alpha-SMA. The development of alpha-SMA coincides with the differentiation of fibroblasts into myofibroblasts that induce wound contraction.

Instability

Shear forces are a major cause of skin graft failure that can disrupt the nascent fragile blood vessel connections. Later, thin skin grafts have less collagen content and are prone to delamination due to shear forces.

Cosmetic issues

Unpleasant cobblestone-like patterns of meshed STSGs are much more prominent than nonmeshed or full-thickness grafts. Color differences are a common problem if donor sites could not be optimally chosen. If excess skin surrounds the grafted area, the skin graft can be excised in multiple steps until primary closure can be reached.

Donor site

Infection at donor sites can occur from bacterial contamination during the operation or in the postoperative period. These infections are treated with topical antimicrobial agents, including silver dressings. The delay in healing of donor sites due to infection can lead to hypertrophic scar formation. Hypertrophic scar or keloid formation can also result from deep donor sites or in patients with a propensity for scarring. Itching is a common reaction to donor sites as well as hypersensitivity to changes in temperature.

Future

Dermal substitutes

Burke *et al.* first described a collagen–glycosaminoglycan scaffold to treat dermal defects in the early 1980s.⁵⁴ Dermal substitutes (Table 15.3) are widely used in large burn injuries, when skin lesions are so extensive and unaffected donor skin areas are often limited. Cadaver skin (allograft) or dermal substitutes can be used initially to cover large defects. Dermal substitutes can also be used to improve functional and aesthetic outcome. Dermal regeneration is very limited in human skin and full-thickness skin defects heal by secondary intention with scar tissue formation. The difference between scar tissue and healthy skin besides the aesthetic appearance is the viscoelasticity and therefore stability. Scar tissue shows histological parallel-oriented collagen fibers, while healthy dermis consists of randomly oriented collagen fibers. In some patients and for restricted donor sites, keratinocyte cultures or very thin STSGs can be attempted to close full-thickness defects. The resulting skin is usually fragile and dry, leading to reopening and ulcers through normal mechanical friction. This poses a particular problem if functional structures underlie the new thin skin. The introduction of the first commercially available skin substitute, Integra®, is a bovine-derived collagen type I cross-linked matrix with glycosaminoglycans that is similar to the dermal structure and covered by a silicone

Table 15.3 Permanent and temporary dermal and epidermal skin substitutes

Product	Tissue – cells	Manufacturing availability	Origin
Epicel® (Genzyme, MA)	Epidermis – cultured epidermal autograft (CEA) sheets	Tissue cultures expanded in the laboratory over several weeks	Autologous and xenogeneic (residual amounts of murine cells)
ReCell® (Avita Medical, UK)	Epidermis – autologous epidermal cells Dermis – fibroblasts; cell suspension, delivered with a spray	Bedside approach (about 30 minutes required)	Autologous
Cellutome™ Epidermal Harvesting System (KCI, TX)	Epidermis – autologous epidermal islands delivered on a dressing	Bedside approach (about 60 minutes required)	Autologous
Integra® (Integra Lifesciences, NJ)	Dermis – bovine tendon type I collagen and glycosaminoglycans on a silicone sheet	On the shelf	Xenogeneic
MatriDerm® (MedSkin Solutions Dr. Suwelack, Germany)	Dermis – bovine acellular non-crosslinked, coated with elastin	On the shelf	Xenogeneic
Alloderm® (LifeCell Corporation, NJ)	Dermis – human acellular lyophilized cadaver dermis	On the shelf	Allogeneic
Dermagraft® (Organogenesis, MA)	Dermis – human fibroblasts on polyglycolic–polylactic acid mesh	On the shelf	Allogeneic
EZ Derm (Mölnlycke Health Care, Sweden)	Dermis – porcine aldehyde cross-linked dermal collagen	On the shelf	Xenogeneic
Oasis® Matrix (Smith and Nephew, TN)	Dermis – porcine acellular small intestine submucosa	On the shelf	Xenogeneic
Allograft	Composite – cryopreserved cadaveric skin	On the shelf	Allogeneic
Apligraf® (Organogenesis, MA)	Composite – neonatal human fibroblasts in bovine type I collagen Neonatal human keratinocytes	On the shelf	Allogeneic/xenogeneic

sheet to recreate temporarily the function of the epidermis. Integra® can be applied to a vascularized wound bed followed by blood vessels and cell growth into the collagen matrix to create a vascularized neodermis after 2–3 weeks. During the avascular period, the dermal graft is very sensitive to infection, one of the main disadvantages of the two-step strategy.

Once revascularization is accomplished, the silicone layer can be removed and the epidermal replacement can be granted by either keratinocyte cultures or a thin STSG (Fig. 15.15). To improve dermal graft integration, surgeons have successfully seeded dermal substitutes with keratinocytes.²³ Newer clinical studies show that small areas of exposed tendon or bone without remaining peritendineum or periosteum can be successfully grafted with Integra®.

After the invention of Integra®, a number of other human- and animal-derived dermal substitutes are now commercially available. Another synthetically engineered dermal substitute is MatriDerm® (MedSkin Solutions Dr. Suwelack), a bovine-derived collagen matrix with noncross-linked collagen fibers of types I, III, and V matrix coated with elastin fibers. Synthetic dermal substitutes such as Integra® and MatriDerm® are permanent dermal regenerative templates that will be ultimately covered by an epidermal autologous graft. For temporal coverage of large wounds, dermal allografts or xenografts are available (see Table 15.3). Allografts and xenografts will be rejected by the recipient and may adhere in patients with large burn injuries for several weeks because of the post-traumatic immunosuppressed stage. After 2–3 weeks dermal

dressings will be removed and a well-vascularized wound bed is found underneath that is ready for final skin reconstruction by autologous grafts. Infection of the acellular dermis demands careful wound dressing and infection control. Another drawback for human- and porcine-derived dermis is possible viral infection transmission.⁵⁵

Cell cultures

Epithelial cell culture autografts were first introduced by Rheinwald and Green in 1975 and pose a milestone in skin regeneration.⁵⁶ In patients with extensive burns, donor sites are often limited. Cultured epithelial autografts (CEA) are keratinocytes harvested from a small biopsy of the same patient that are then expanded manifold in the laboratory (Fig. 15.16).

The time needed to expand keratinocyte cultures *in vitro* for clinical use is dependent upon the delivery method. In order to obtain sheets of confluent keratinocytes as in normal epidermis, it may take up to 5 weeks. This time can be shortened to less than 2 weeks⁵⁷ by expanding the cultures on bioscaffolds that allow cell attachment and proliferation prior to transplantation. Hyaluronan or collagen scaffolds have been demonstrated to be very useful in delivering cell-seeded sheets with approximately 80% confluence up to even multi-layered epithelial tissue constructs. Cell suspensions have the advantage of being delivered faster, reducing the *in vitro* time to only 5–7 days. Recently, ReCell® (Avita Medical), invented

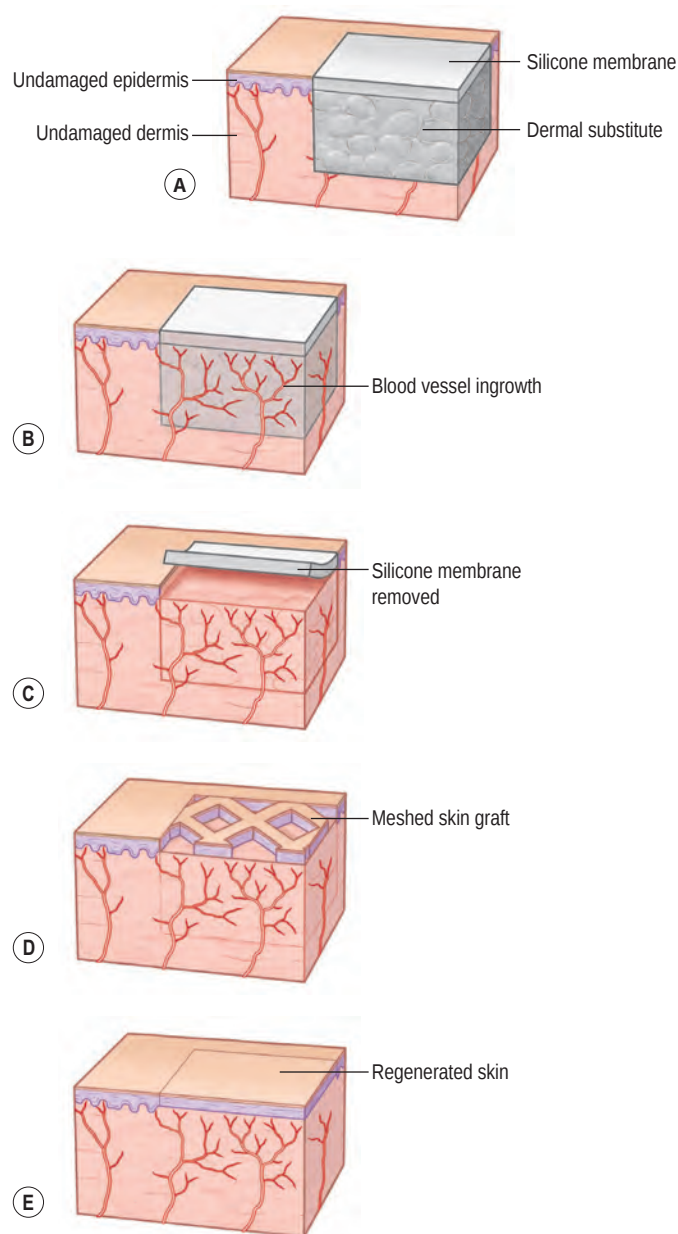


Fig. 15.15 Skin regeneration with dermal substitutes. If large, deep skin defects have to be covered with thin split-thickness skin grafts, dermal substitutes can be used to augment the dermal layer and therefore the aesthetic and functional outcome. (Adapted from www.integra-ls.com.)

by Fiona Wood *et al.*, introduced an even faster method, applying noncultured keratinocytes in a one-step procedure.⁵⁸ Since in deep wounds time is a critical issue, this strategy, offering accelerated delivery, is promising, although still poorly characterized. One major concern is whether cells directly sprayed on the wound surface are able to find attachment sites to engraft and survive. Another bedside approach for epidermal graft is represented by the Cellutome™ (KCI, TX), which allows for harvesting epidermal islets down to the basal layer. The islets are then transferred on the recipient wound via a dressing and the donor site heals spontaneously in a few days.

The introduction of CEA in clinical practice dates back more than 20 years, but the best delivery method, as well as

efficacy and indications, has not been identified yet. Published studies have reported take rates of CEA on biomaterials varying from 0 to 80%, raising many questions about their effectiveness. Boyce *et al.*⁵⁹ described bilayered autologous skin constructs with keratinocytes and fibroblasts on collagen-glycosaminoglycan matrixes that showed promising results in burn treatment. Direct comparison of autologous bilayered skin constructs versus STSGs showed higher initial nontake rates and regraftment after treatment with the skin construct, while STSG-treated areas healed spontaneously. Once wound closure occurred, the outcomes showed similar results in skin quality at longer time points. The variability may be explained by heterogeneous wound cohorts, inconsistencies in the time at which wounds were analyzed, treatment techniques, and measuring systems.

Bioengineered cultured allogeneic bilayered constructs

Cell-seeded skin constructs were first described in the early 1980s, when autologous keratinocytes and fibroblasts were

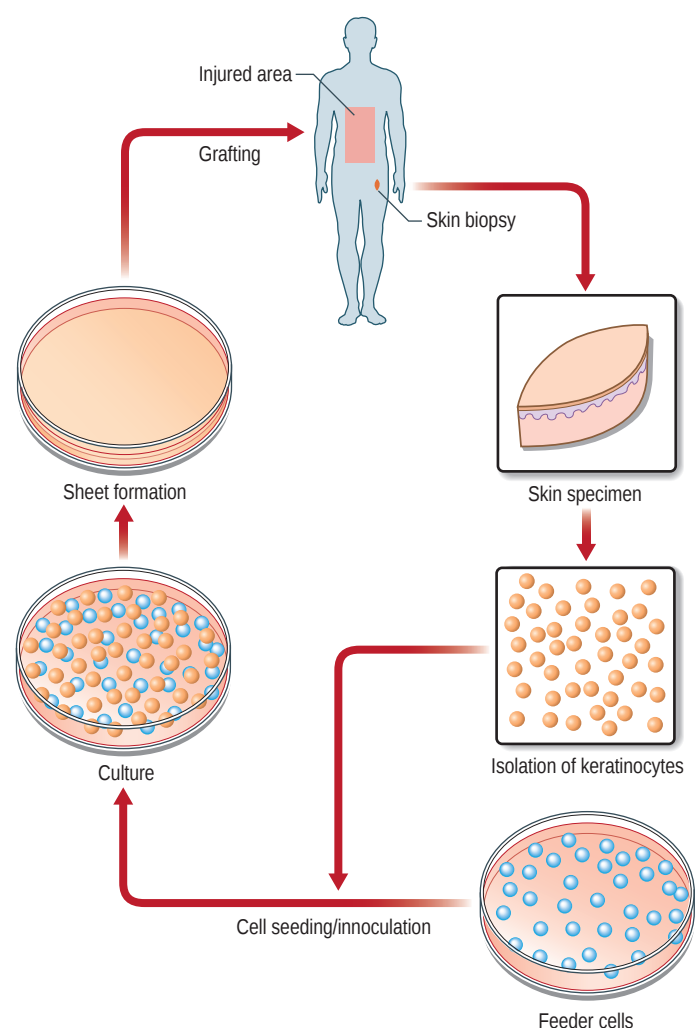


Fig. 15.16 Keratinocyte cultures. Epidermal cells can be harvested from a small biopsy from the patient and expanded manifold *in vitro*. Once the expansion is achieved the autologous keratinocytes can be delivered back to the patient. (Adapted from *Autologous Cultured Epidermis*, www.jpte.co.jp.)

seeded into collagen glycosaminoglycan matrixes by centrifugation.⁶⁰ Further research found neonatal skin cells to be very efficient in accelerating wound healing. Neonatal foreskin keratinocytes and fibroblasts were then used in combination with biological or synthetically engineered scaffolds to stimulate wound healing in topically applied allogeneic skin constructs. Other than autologous cells, which seem to integrate into wound tissues, allogeneic constructs rather stimulate healing by growth factor release and initial production of extracellular matrix proteins, but are rejected eventually. Apligraf® (Organogenesis, Canton, MA and Novartis Pharmaceuticals, East Hanover, NJ) is a bilayered living skin equivalent composed of type I bovine collagen and allogeneic

keratinocytes and fibroblasts obtained from neonatal foreskin. Fibroblasts are cultured in the collagen matrix where they proliferate and augment the extracellular matrix with all types of proteins. Keratinocytes are then added and build up the epidermal layer. The living skin construct supports skin graft take in difficult wounds, such as burn wounds, or accelerates healing in chronic wounds. With a shelf-life of 5 days at room temperature, Apligraf® has to be applied fresh either as a temporary dressing or over meshed STSGs.

Future products that are less immunogenic might be useful for improving skin regeneration, and novel technologies such as 3D printing will soon make clinically available more sophisticated synthetic constructs.



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Tissue engineering

Andrea J. O'Connor, Diego Marre, Kiryu K. Yap, Daniel E. Heath, and Wayne A. Morrison

SYNOPSIS

- Tissue engineering, i.e., a growth of three-dimensional (3D) tissues using cells, scaffolds, and blood supply, calls on the skills and expertise of cell biologists, engineers, and clinical surgeons.
- It aims to replicate the embryological process of tissue regeneration rather than adult healing and, given the complexity of the process, much of our effort to date may seem simplistic.
- Nevertheless, much progress has been made across the full spectrum of the research field. This chapter outlines the historical beginnings of tissue engineering and discusses the current status, addressing the three structural components of tissue: cells, matrix, and vascular supply.
- Biomaterials science and applications are discussed as well as an overview of emerging technologies in the field.
- Much of the work in tissue engineering has been performed *ex vivo* and unfortunately many of these experiments do not predict the fate of cells and matrices *in vivo*.
- Models of *in vivo* tissue engineering are discussed along with the progress in specific fields.
- Very few clinical trials have been undertaken, controls or placebo groups are difficult to incorporate in trial design, and tracking the fate of implanted cells is difficult in humans.
- All this needs to be viewed with the perspective that, to date, very few truly tissue-engineered products have come to market despite huge expectations and investments.

Introduction

Traditional reconstructive plastic surgery techniques “rob Peter to pay Paul”. The long-held hope for the ultimate reconstruction has been allotransplantation but to date drug morbidity makes the risk-benefit ratio unfavorable for non-vital organs except in rare circumstances. Tissue engineering has emerged as a possible new direction where ideally our own body is stimulated to generate its own replacement tissue.

Definition of tissue engineering

The definition of tissue engineering quoted by most authors is that it is “an interdisciplinary field that applies the principles of engineering and the life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function”.¹ It stressed the key roles of engineering techniques, material science, biochemical expertise, and cell biology. What it did not stress was the role that blood supply would play if and when such engineered tissues were to be transplanted into the body. It is to this piece of the tissue-engineering puzzle that plastic surgeons may hold the key and why the clinical application of tissue engineering will become the province of the plastic surgeon.

Regenerative medicine

While tissue engineering has predominantly surgical roots with research directed by cell biologists and engineers, regenerative medicine, a modernized branding for cellular therapy, was the province of physicians and cell biologists. It has since expanded to target organ regeneration and there is now considerable crosstalk between the disciplines. For the purpose of this chapter, we distinguish tissue engineering as the pursuit of 3D structural tissue generation.

The classical paradigm of tissue engineering followed Jack Burke’s artificial dermis skin model of seeding cells on to a biodegradable matrix scaffold and implanting it into a vascularized bed.² This would rapidly nourish the graft and, by a combination of survival of implanted cells and substitution, the “new skin” would become functional. Clinical needs for bone and cartilage determined early research directions and this gave pre-eminence to the engineering materials side of the tissue-engineering pendulum as structural load, stability and ideally biodegradability were clearly essential. The spectacular image of the “human ear” in the mouse (Fig. 16.1) galvanized scientists and the public alike as to the potential offered by tissue engineering and reinforced the dogma of expanding cells in culture, seeding them *ex vivo* into scaffold



Fig. 16.1 “Human ear in the mouse”: cultured bovine cartilage cells seeded on a PLGA scaffold in the shape of a human ear and implanted in the back of a mouse. (Reproduced from Cao Y, Vacanti J, Paige K, et al. *Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear*. *Plast Reconstr Surg*. 1997;100:297–302.)

matrix and implanting the composite into the body.³ The journal *Tissue Engineering* was established in 1996 and many publications focused on novel synthetic biomaterials attempting to replicate pore size and connectivity of nature’s extracellular matrix (ECM) using sophisticated machinery and mathematical modeling. Toxicity, structural integrity, biodegradability, surface modifications, cell survival, adherence, migration, and proliferation could all be tested in *ex vivo* models. Bioreactors could greatly expand cell numbers and mimic *in vivo* physical environments to allow more sophisticated *ex vivo* experimentation.

The *ex vivo* paradigm stumbled when attempts were made to translate advances into the living animal. Biomaterials proved toxic to cells in some cases and acted as foreign bodies.⁴ Their dynamic structural behavior was very different to *ex vivo* testing and cells found life hostile in the new world. Despite the obvious need for multidisciplinary cooperation, most early research was directed in isolation and this has led to delayed progress in tissue engineering. The engineer’s mindset is focused on scaffold structure, tensile strength, biocompatibility, and surface modification while the cell biologist’s is on cell identification, expansion, and differentiation. Scaffold modeling was based on sophisticated replication of human ECMs with respect to pore size, but evaluation was largely done *in vitro*. Both teams are laboratory-based, observing cell responses outside the living animal, and had limited access to a practicing clinician’s observations, especially plastic surgeons, with respect to the behavior of foreign bodies *in vivo*. Furthermore, surgeons know from bitter experience with skin grafting that cells seeded on to an implanted scaffold *ex vivo* and then implanted are unlikely to connect to a blood supply in sufficient time to avoid ischemic death. Vascularization is vital to cell survival and is a key to any successful multidisciplinary partnership towards clinical translation of tissue engineering. Unfortunately, early tissue engineers were beguiled by selecting tissues that were very thin, such as skin, which could rapidly connect to a blood supply or tissue that did not need a blood supply, namely cartilage. Once 3D soft tissues were attempted, it became evident that cell survival was poor and that blood supply was paramount.^{5–7}

Embryology

Tissue engineering at its core is an attempt to replicate embryology or fetal healing. Here, new tissues form in response to certain signals, both biochemical and biomechanical.⁸ The tissues are determined or patterned according to a genetically guided time sequence where growth factors and their chemical gradients as well as changing physical forces in the matrix attract, guide, and differentiate primitive cells into functional clusters. In this process, cells will link with a capillary bed, lay down their own matrix, and create an environment appropriate to their expansion and development. This relatively new concept of “self-assembly” is important to appreciate when translating embryogenesis into a model for tissue engineering. As cells change their phenotype, for example, from precursor to differentiated or from motile and proliferative to resting and clustered, their ECM requirements alter accordingly. Many cells secrete their own matrix suitable to their needs. This constant change cannot easily be replicated in the laboratory and it is simplistic to believe we can seed cells on to one specific matrix and assume this will be appropriate for the cells’ needs throughout their development *in vivo*, nor is it easily conceivable that “smart surfaces” can be imprinted on synthetic matrices in layers programmed to be released according to the changing cells’ needs when at this point we do not know what these needs are.

Examples from nature

Nature has given us many examples of spontaneous tissue regeneration or engineering which give clues to how this might be modeled artificially. The liver has been known since ancient times to self-regenerate and is captured in the legend of Prometheus, a Titan, who stole fire from Zeus and gave it to mortals. As punishment, he was bound to a rock while a great eagle ate his liver each day, only to have it grow back to be eaten again.

A salamander regrows its legs, the fetus repairs wounds with minimal scarring, and humans have the capacity to gain and lose adiposity rapidly. Ruptured tendons can regenerate across gaps when their ends are retained within their synovial sheath where their matrix and cellular environment are maintained and axial mechanical force signals are transduced into biochemical stimulation (Fig. 16.2). Muscles also will regenerate across gaps in the same way.

Access the Historical Perspective section, including Fig. 16.3, online at <http://www.expertconsult.com>

Components of tissue engineering

Adult wound healing involves deliberate sloughing of damaged tissue and repair by rapid wound closure, scar, and contracture. A primary goal of tissue engineering is to achieve a more scarless regeneration through the use of stem cells, matrix, and growth factors delivered according to a sequence and type learned from embryology, as described above.

Simplistically, our tissues can be viewed as a composite of: (1) cells (both parenchymal and stromal); (2) matrix; and (3) blood vessels. Each of these components must be considered

Historical perspective

The term “tissue engineering” was coined at a meeting sponsored by the National Science Foundation in 1987. Implied in the definition of tissue engineering is the use of living cells, biomolecules, and/or biomaterials.⁹ One of the earliest human applications of the concepts of tissue engineering is in oral surgery with what is termed “guided bone regeneration” (GBR) or guided tissue regeneration (GTR).¹⁰ This surgical procedure utilizes barrier membranes to direct growth of bone and soft tissue and is predominantly applied in the oral cavity to support new bone growth on alveolar ridges to allow stable insertion of implants.¹¹ The membrane which is inserted under the mucoperiosteum creates a dedicated space that collects the raw ingredients of osteogenesis – periosteal and bone-derived osteoblasts, vascular cells, tissue fluid, and matrix secretions appropriate for the biochemical signaling of bone formation. The rigid surface of a membrane induces biomechanical signals to the cells to proliferate and migrate along its surface. Platelet-enriched plasma is sometimes added to enhance tissue growth by augmenting the growth factor profile.¹²

Similar phenomena are observed with “distraction osteogenesis”, where long bones are osteotomized within their periosteal sleeve and slowly distracted (Fig. 16.3). The

expanding space spontaneously fills with new bone. Just as in GBR, the environment within the newly created space is exclusively conducive to bone formation. Both GBR and distraction osteogenesis are examples of what would now be called endogenous or intrinsic tissue engineering, where the body grows its own tissue in response to local signals of trauma, ischemia, inflammation, and mechanical forces which promote vascularization followed by specialized tissue regeneration.

Cancellous bone grafting, first described by the New Zealand plastic surgeon Rainsford Mowlem,¹³ is an even earlier example of a tissue-engineering concept, in this case using the extrinsic principle where a scaffold loaded with cells is implanted into a new site. Most of the cells probably die but the bone matrix survives and acts as a scaffold with the appropriate signals to attract new blood vessel and bone-forming cells into its interstices and replace it by “creeping substitution”. The bone remodels according to the biomechanical forces of its new environment, as articulated by Wolf’s law. Bone regeneration has also been encouraged by the implantation of synthetic porous scaffold materials such as Proplast and more recently MEDPOR, usually primed with autologous blood to attract ingrowth of endogenous tissue.

As stated previously, tissue engineering and regenerative medicine are conceptually different but both disciplines now borrow from each other’s progress.

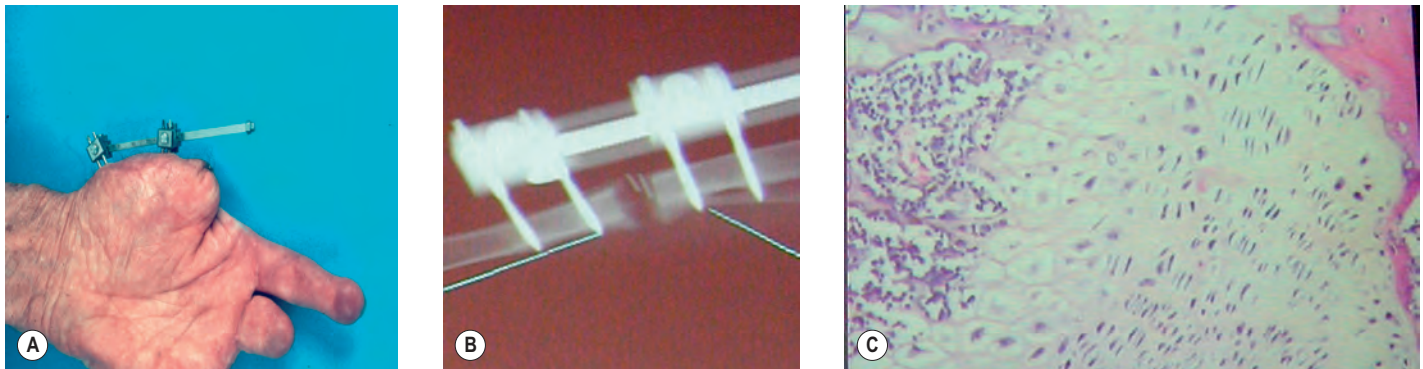


Fig. 16.3 (A) Thumb stump with distraction device. (B) X-ray of bone distraction. (C) New bone filling the gap.

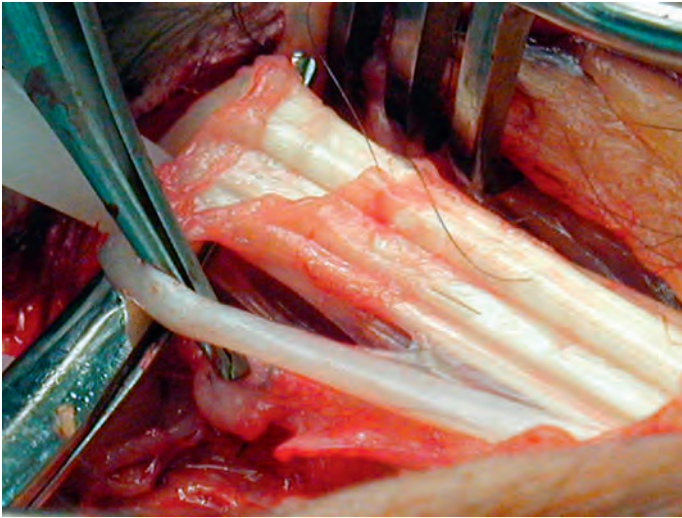


Fig. 16.2 Spontaneous regeneration of ruptured extensor digiti minimi tendon at the wrist (lower tendon held with forceps).

in the context of tissue engineering as cell maintenance and behavior including growth and regeneration are influenced by biochemical and biomechanical interplay. Furthermore, the development of a functional tissue must be vascularized to ensure survival of the neotissue. Each of these components is the purview of the tissue engineer.

Cell sources for tissue engineering

Cells used for tissue engineering may be autologous, heterologous, or xenogeneic and each type may be mature differentiated or in precursor stem cell form. Ideally, cells for tissue engineering should be our own cells, and endogenously mobilized to participate in the regenerative process, thereby avoiding issues of rejection and *ex vivo* cell processing or manipulation. This is in essence wound healing, where key cells, both local and distant, are mobilized in response to biochemical gradients and biomechanical forces. Although this endogenous repair is ideal it is, unfortunately, not often realized.

Instead, early tissue engineering strategies relied on the collection of the cell type of interest from the patient, *ex vivo* cell expansion, and then reimplantation into the patient, usually in conjunction with a tissue engineering scaffold support. Many cell types such as chondrocytes for cartilage, osteocytes for bone, Schwann cells for nerves, and fibroblasts for ligament and tendon engineering are highly proliferative in culture and were early tissue engineering candidates. All these cells have significant proliferative potential *in vitro* but, once implanted, assuming they survive, are not expected to expand further. However, other differentiated cells such as adult cardiomyocytes, hepatocytes, and adipocytes are infamously difficult to culture and expand *in vitro*, significantly limiting the application of this tissue engineering approach. A second challenge with this early model of tissue engineering is that collection of the patient's primary cells requires biopsy of the patient's tissue which is, at best, uncomfortable and, at worst, impossible due to the diseased state of the tissue.

To circumvent these roadblocks, today's tissue engineers will more likely utilize stem cells that can be expanded and differentiated *ex vivo*. There are multiple types of stem cells that have been explored including embryonic, adult, and

induced pluripotent stem cells. Here we will discuss embryonic stem cells and then focus on stem cell types most relevant to the plastic surgeon, the sources of cells, their advantages and disadvantages and briefly discuss their use in tissue engineering.

Embryonic stem (ES) cells

Embryonic stem (ES) cells are totipotent, infinitely proliferative, and can be differentiated into all tissue types. However, they are also unstable and form teratomas. Additionally, their sourcing and utilization are limited by ethical/legal concerns. Successful differentiation protocols have been found to induce ES cells along specific lineage pathways from all germ layers towards many specific tissues and organs.¹⁴ These cells are probably immunogenic and ethical issues will persist. There are many regulatory and organizational issues that will make pathways into the clinic difficult for elective procedures such as tissue engineering, especially proving that they will not form cancer.

Adult stem cells

Adult stem cells are multipotent and limited in their proliferation capacity and differentiation potential. They are collected and expanded from tissue biopsies through variations on a process referred to as the colony forming unit (CFU) assay.¹⁵ These progenitor cells are present at low frequencies in the patient samples, often approximately 1 progenitor cell/100 000 nucleated cells (though the prevalence of adipose-derived stem cells is significantly higher). The tissue sample is processed to remove some of the contaminating cells, and the remaining mononuclear cells are then plated onto tissue culture plastic. The progenitor cells are then isolated and purified by their ability to adhere to the substrate and proliferate. Non-adherent cells are removed and the medium is supplemented with factors that promote the survival and growth of the cells of interest. Over two to three passages the experimenter is left with a relatively pure population of stem cells.

Two of the first documented adult stem cells were both found in bone marrow: (1) hematopoietic stem cells (HSCs), which differentiated into the white blood cell population and (2) mesenchymal stem cells (MSCs), the progenitors of bone, cartilage, fat, and muscle.^{16,17} Additionally, endothelial progenitor cells (EPCs) have been isolated and cultured from adult peripheral blood.¹⁸ Furthermore, MSCs and EPCs are now known to be present not only in bone marrow but also in fat tissue associated with the microvasculature,¹⁹ where they are known as adipose-derived stem cells (ASCs). In more recent years, tissue-specific stem cells have now been isolated from almost every organ as well as mesenchyme and include cardiac, liver, lung, kidney, brain, breast and others. Here we focus on the adult stem cells that are of most use to the plastic surgeon: the mesenchymal stem cell, the adipose-derived stem cell and the endothelial progenitor cell.

Mesenchymal stem cells

Classically, MSCs were derived from bone marrow and used as connective tissue progenitors (cartilage, bone, fat, and muscle). MSCs have the advantage that they do not express MHC class II markers and several studies have suggested they are relatively immune-privileged and may be used as

allografts. This is a potentially attractive concept where cells could be sourced from stem cell banks for tissue engineering.^{14,20} Due to these attractive properties, MSCs have become a favored source of cells for the engineering of mesenchymal tissues, the main building blocks employed for plastic and orthopedic reconstruction.

Due to their immune-privileged status, many researchers are attempting to expand upon the utility of MSCs. One avenue of research is differentiating these cells into cell types that originate from different germ layers. Furthermore, researchers have searched for MSCs in other more readily accessed tissues that can be isolated through less invasive means. Mesenchymal stem cell-like cells have been observed in a variety of tissues including skin, muscle, umbilical cord, placenta, corneal stroma, and dental pulp of deciduous teeth. However, all of these sources produce progenitor populations with nuanced differences in their proliferation and differentiation potential with bone marrow-derived MSCs remaining the most understood of MSC-like cells available.

MSCs injected as a form of cellular therapy have been widely explored for a variety of conditions including cardiac disease, peripheral vascular disease, and irradiation injury in humans. Additionally, a large amount of experience in the horseracing industry boasts survival, differentiation, and function of such cells. However, few of these studies were controlled and tracking of cells was absent or difficult to assess. With the exception of brain, almost no cases could confirm that the MSCs survived in significant numbers or that these survivors differentiated into the injured tissue type. Interestingly, there is a growing body of knowledge that suggests MSCs injected as a form of therapy do not aid recovery through direct incorporation with damaged tissue. Most studies now concede that the paracrine-growth factor-hormonal-cytokine immune-modulatory effects probably account for the benefits seen with these stem cells. For example, ischemia increases homing of these cells to the injured site where MSCs release high levels of vascular endothelial growth factor (VEGF) to modulate the repair of capillaries. Additionally, MSCs injected intravenously in cardiac infarct models do not implant in the heart nor become heart tissue but lodge in the lung, where they are activated to secrete the anti-inflammatory protein TSG-6,²¹ and it is probably the anti-inflammatory factor that induces the beneficial effects. More recently, MSCs have been used as intravenous infusions for the treatment of multiple sclerosis, with promising results. It is felt that the response was anti-inflammatory in nature due to the release of high numbers of M2 anti-inflammatory macrophages.²² Despite the clear evidence that these cells can be used in beneficial cellular therapies, the exact mechanism of action and the best method of employing the cells are still unclear. However, the clinical use of these cells will continue to increase. In fact, the National Institutes of Health of the United States has created a bone marrow stromal cell transplantation program prepared from bone marrow of healthy subjects to treat patients with inflammatory bowel disease, cardiovascular disease, and acute graft-vs-host disease.²³

Adipose-derived stem cells

Due to their abundance and ease of harvest by liposuction, adipose-derived stem cells are a preferred autologous stem cell source. This cell type has similar properties to bone marrow-derived stem cells but is more abundant, more easily

cultured, grows more rapidly and can be cultured for longer periods than bone marrow stem cells before senescence. While bone marrow-derived mesenchymal stem cells are present at extremely low frequencies, one gram of adipose tissue can yield 5000 stem cells making fat a much richer source of stem cells than bone marrow.²⁴ Additionally, some studies have illustrated that the ASC population may also have low immunogenicity.^{25,26} Interestingly, the ASCs are not thought to be a pure cell population, and for tissue-engineering and fat injection purposes, it is clear that obsessive attempts to isolate the “pure ASC” may be counterproductive as the other cells, especially the EPCs, may also contribute to the apparent functional effects of stem cells.

As with MSCs, cellular therapies utilizing ASCs have shown promising results. Partially purified ASCs which still retain CD34 and CD90 markers grown into spheroid clusters in a gel culture system differentiate into endothelial cells and capillary structures in methyl cellulose and these produce high levels of VEGF. They also rapidly differentiate into adipocytes in adipogenic media, making them potentially suitable for adipose tissue engineering.²⁷ Other growth factors released from ASCs include macrophage colony-stimulating factor, GM-CSF, VEGF, anti-apoptotic factors, hepatocyte growth factor, and transforming growth factor- β (TGF- β). In hypoxia, the VEGF levels are significantly increased, leading to angiogenesis and decreased apoptosis.

Endothelial progenitor cells

A major requirement in tissue engineering is the incorporation of a functional vasculature network in the neotissue. One cell type that shows promise in this arena is the endothelial progenitor cell (EPC). These cells were first identified in 1997 by Asahara *et al.*,²⁸ are present in adult circulation, and autologous cells can be isolated and expanded from peripheral blood collected through simple venipuncture. Subsequent research has illustrated there are actually two distinct EPC populations that participate in vascular repair and angiogenesis via different mechanisms. The first population, referred to as circulating angiogenic cells (or colony forming unit–Hill cells) are not believed to directly incorporate into the endothelium; instead, they are posited to support resident endothelial cells through paracrine signalling. Endothelial colony forming cells (ECFCs), on the other hand, have been shown to differentiate into cells with endothelial phenotype and to regenerate an endothelial cell population.¹⁸ Both cell types can be used to promote autologous endothelialization.

Challenges associated with adult stem cells

Adult stem cells are advantageous in tissue engineering as they provide an autologous and/or non-immunogenic source of cells. However, they are not without limitations. Adult stem cells display patient-to-patient variations in their prevalence, proliferative capacity, and differentiation potential.^{29–31} Additionally, their utility is also a factor of age and disease state of the donor. Furthermore, during *ex vivo* expansion, cells may exit the cell proliferation cycle (prematurely senesce) or prematurely lose differentiation potential.^{32,33}

Induced pluripotent stem cells

One of the most exciting discoveries in stem cell science occurred in 2006 when Takahashi *et al.*³⁴ described a method

of converting murine somatic fully differentiated skin cells, mostly fibroblasts, to an embryonic-like state using four transcription factors. The achievement was then repeated in 2007 for human cells. They are termed induced pluripotent stem (iPS) cells and possess unlimited proliferation capacity and the ability to differentiate into cells from all germ layers both *in vitro* and *in vivo*. Additionally, these cells can be patient-specific, thus present no issues of allogenicity and they are not encumbered by the same legal/ethical concerns as embryonic stem cells. In 2012, human iPS cells were even produced from exfoliated epithelial cells present in urine.³⁵ The major problem associated with the production of iPS cells is that it requires genetic manipulation of the cells. Furthermore, two of the genes used in this process (c-Myc and KLF4) are oncogenes.

Much of the research related to iPS cells in recent years has revolved around improving safety. Specifically, inducing a pluripotent state without genetic modification has been a major goal. Zhou *et al.* accomplished this task in 2009 by delivering the four proteins that the above-mentioned genes code for directly into the cell. Generation of these cells, referred to as protein-induced pluripotent stem cells (piPSCs), bypasses the need for viral or plasmid transfection and reduces the risks of cancer formation.³⁶ A current drawback to this technique is that the efficiency of the protein induction is very low, and research is addressing this limitation. Mice have been cloned from safer versions of their own iPS cells by implantation into an enucleated ovum, and these animals have reproduced and no cancers have been detected.³⁷ Another technological challenge for the utilization of iPS cell technology is that these cells are not immune privileged requiring collection, induction, expansion, and differentiation of autologous cells. This is a costly and time-consuming scenario. The alternative to using autologous cells is to create a bank of iPS cells that can be HLA matched to the patient. Clinical utilization of these cells is being explored. Beyond the realm of tissue engineering, models based on these cells have also become powerful tools for drug discovery and investigations into genetically based diseases.

Cellular interactions with their environment

Many cell types are exquisitely sensitive to stimuli present in the environment. These stimuli are diverse and include soluble molecules, molecular recognition sites present in the solid phase (ECM or biomaterial), interactions with other cells, substrate stiffness and the micro/nano-structure of the surroundings. In this section we consider how these parameters can affect the phenotype and behavior of cells and in the biomaterials section we discuss how this knowledge can be translated into next generation materials for use in tissue engineering.

Soluble signals

Many soluble biomolecules such as metalloproteins, growth factors, and chemokines play vital roles locally and systemically in repair and tissue development. Starting from the earliest stages of life, embryogenesis is critically dependent on growth factor cascades released sequentially according to a genetic code and time clock. In adults these cellular signaling molecules continue to play crucial roles. For example,

inflammatory cytokines and local angiogenic growth factors stimulate endothelial cell migration, proliferation, and mitogenesis and growth factor cytokines signal distant precursor cells, including EPCs.^{10,38} This knowledge has direct impact on the field of tissue engineering, as it is necessary to know the appropriate soluble signaling molecules to maintain cell viability both during culture and *in vivo*, to maintain cellular phenotype, and to drive lineage specific differentiation of stem cells. However, biomolecules such as growth factors are expensive, have short half-lives and angiogenic growth factors have the particular risk of reactivating dormant cancer when used for post-cancer resection reconstruction. The need for local delivery of specific biomolecules at specific concentrations is key to successful tissue regeneration and will be discussed below via biomaterials with controlled release properties.

Matrix signals

In addition to surface receptors that engage with soluble factors, cells also possess receptors such as integrins and syndecans that bind to a variety of ligands present in the extracellular matrix (ECM). Many cell types are adhesion dependent, meaning that if they do not experience biologically specific binding to an external matrix they will not maintain viability. Additionally, the number and strength of bonds with the external matrix affects a wide variety of cellular behaviors ranging from adhesion, focal adhesion formation and migration to morphology. Additionally, the ECM binds and sequesters growth factors that also drive cellular function. Knowledge of the biologically specific binding that occurs between cells and their matrix has resulted in the development of biofunctionalized materials that can promote specific cell functions.

Intercellular signals

Cells also interact with neighboring cells in both native tissue and in *ex vivo* culture. These interactions can occur through two main methods: direct contact via receptors such as cadherins and soluble signaling through paracrine factors. In traditional cell culture, single populations of cells are grown in isolation, implanted and rely on recruitment of supporting cellular structures and matrix to evolve into a stable, functional tissue. However, co-culturing cells with other types prior to implantation can facilitate their survival and function, such as endothelial cells for vasculature,³⁹ MSCs for paracrine effects or for their ability to incorporate into developing tissues *in vivo* like blood vessels¹⁹ and beating cardiomyocytes with ASCs *in vitro* to initiate differentiation into cardiac lineage.⁴⁰

Mechanics and structure of the environment

In addition to biological signaling that arises directly from a receptor binding to a ligand, cells also respond to the mechanical properties and dimensionality of their environment. The cell measures the flexibility of its substrate cytoskeleton myosin push/pull on the focal adhesion. The response then leads to changes in tyrosine phosphorylation to signal transduction to the nucleus. *In vivo*, this phenomenon is commonly observed during events such as embryonic development and wound healing⁴¹ as synthesis/degradation of ECM proteins,

movement of cells, or fluid shear from blood flow modulate the mechanical properties of the cells' environment.

The mechanical properties of tissues and their components vary widely (Table 16.1 and Fig. 16.4A) and so the physical microenvironment of particular cells *in vivo* also varies significantly. In traditional cell culture, cells are grown on rigid and two-dimensional tissue culture plastic, the equivalent of cells being firmly stretched in clinical situations. They then move, migrate, and proliferate until they reach confluence. The same cells when placed in a soft 3D culture gel environment sense a modulus that encourages the cells to cluster together into spheroids (Fig. 16.5). When the cells pull on the soft matrix they pull it into a ball, stop dividing, and many apoptose. If they are stem cells the stiffness of the environment may promote lineage-specific differentiation.^{42–44} Engler *et al.*^{44,45} have shown that MSC lineage specification can be altered *in vitro* when cells are cultured on substrates of different stiffness (see Fig. 16.4). Cellular morphology, gene expression, migration, and proliferation are also modulated by the mechanical properties of their microenvironment.^{43,46–48}

The response of cells to environmental stiffness and dimensionality provides the tissue engineer with an additional tool that can be used to direct cell function. For example, chondrocytes change morphology and lose their chondrogenic capacity in 2D monolayer culture but can maintain these features in 3D culture.⁴⁹ The response of cells to mechanical stimulation is used in tissue engineering strategies such as distraction osteogenesis. Periods of stretch promote proliferation and migration while relaxation incites cells to cluster together and terminally differentiate into bone. Guided tissue regeneration similarly works by presenting the cells with a hard surface that stimulates them to divide and to migrate.

Stem cell mechanobiology is attracting increased attention as understanding develops of the influence of substrate mechanics and architecture on differentiation.⁴⁵ Cells may be cultured in 3D on biomaterial supports such as porous scaffolds, hydrogels, or microspheres under conditions designed for the desired cell attachment, migration, proliferation, and differentiation.^{50,51} This knowledge can influence the development of new biomaterials with tailored properties and direct the fabrication of these materials into three-dimensional scaffolds to maximize the healing process.

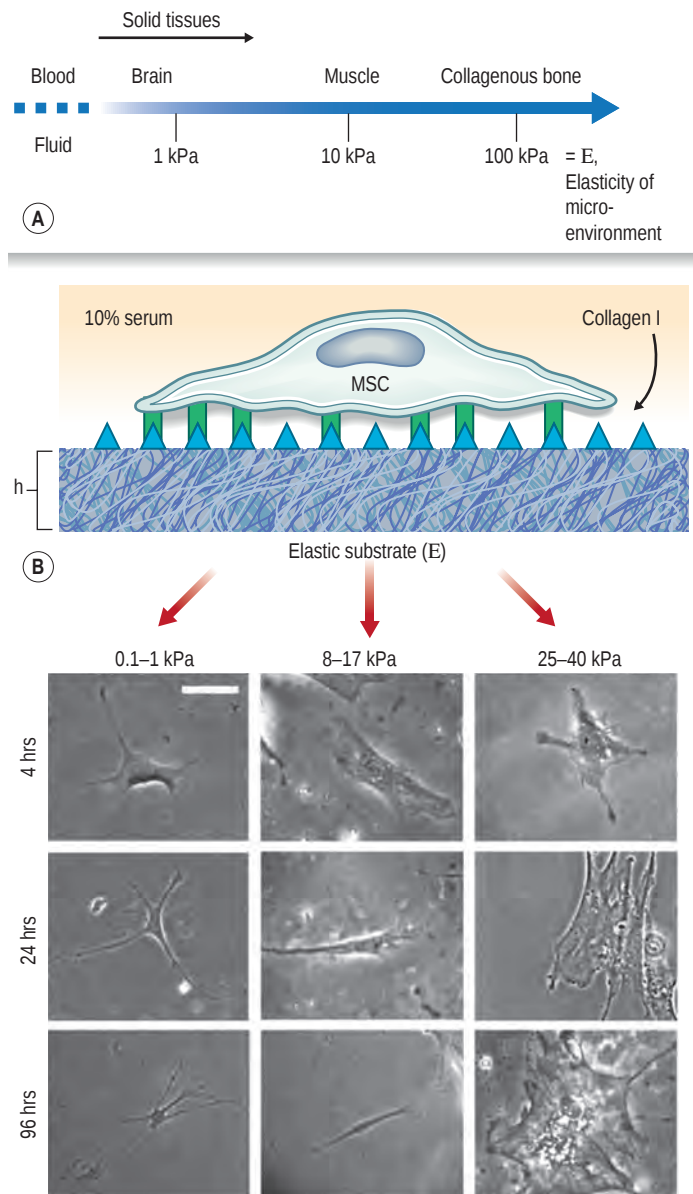


Fig. 16.4 Effects of substrate mechanical properties on differentiation. **(A)** Range of microenvironment elasticity for various solid tissues. **(B)** Mesenchymal stem cells (MSCs) grown on collagen I-coated hydrogels of various elastic moduli differentiate to phenotypes corresponding to tissues of the same elasticity as the hydrogels. (Adapted From Engler AJ, Sen S, Sweeney HL, et al. *Matrix elasticity directs stem cell lineage specification*. Cell. 2006;126:677–689.)

Table 16.1 Typical mechanical properties of selected tissues and tissue components

Material	Elastic modulus	Yield stress	Maximum strain
Elastin	100kPa	300 kPa	300%
Cartilage	10 MPa	8–20 MPa	70–200%
Skin	35 MPa	15 MPa	100%
Muscle fascia	350 MPa	15 MPa	170%
Tendon	700 MPa	60 MPa	10%
Cortical bone	17.4 GPa	160 MPa	1.8%

(Adapted from Palsson BO, Bhatia SN. *Tissue Engineering*. Upper Saddle River, NJ: Pearson Education; 2004; and Cowin SC. The mechanical properties of cortical bone tissue. In: Cowin SC (ed). *Bone Mechanics*. Boca Raton, FL: CRC Press; 1989.)

Biomaterials used in tissue engineering

In addition to cells, a main component of solid tissues is the extracellular matrix which provides structure and biochemical signals to the cells. However, when cells are expanded outside the body, they typically grow in monolayers, not the intricate patterns of a fully realized three-dimensional tissue. Therefore, cells are often seeded onto a 3D scaffold. In this light, biomaterial scaffolds can be thought of as artificial ECMs. Here we discuss the main classes of biomaterials for tissue engineering and methods employed to create materials that drive desired cellular behaviors.

Many criteria exist for biomaterials to be suitable for tissue engineering applications, as outlined in Box 16.1. A wide

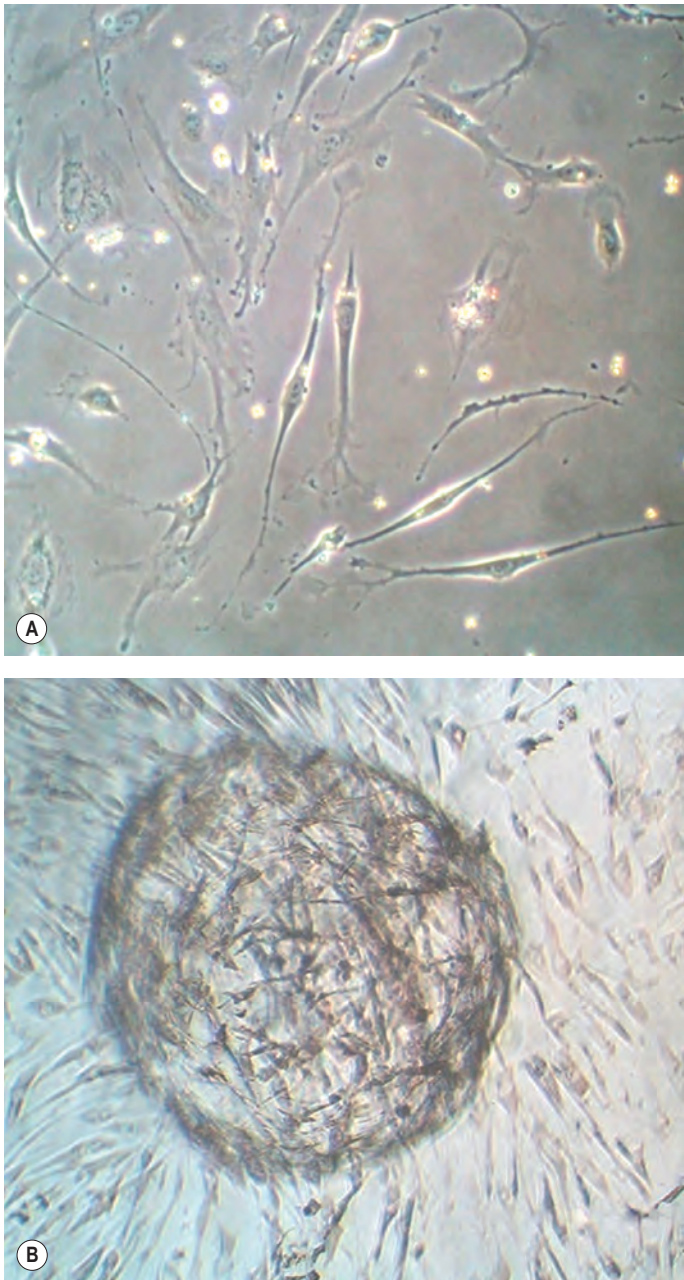


Fig. 16.5 (A) Preadipocytes growing on two-dimensional tissue culture plastic. (B) The same cells growing in three-dimensional gel culture form spheroids. (Reproduced from Stillaert FB, Abberton KM, Keramidaris E, et al. *Intrinsics and dynamics of fat grafts: an in vitro study*. *Plast Reconstr Surg*. 2010;126: 1155–1162.)

variety of synthetic and naturally derived biomaterials have been considered to meet these needs although they do not generally ideally satisfy all of these criteria.⁵² Early tissue-engineering attempts tended to utilize materials that had already been used in other clinical applications, such as the polymers used in degradable sutures, or natural materials such as coral, alginate and collagen. More recently, numerous alternatives have been formulated as researchers aim to develop multifunctional biomimetic biomaterials to suit the specific demands of tissue engineering, which can differ significantly from those of other biomaterial applications. New materials require extensive testing *in vitro* and *in vivo* before

BOX 16.1 Criteria for biomaterials to be suitable for tissue engineering applications

Biocompatibility, i.e., eliciting a suitable host response in the specific application. Suitable mechanical properties for target tissue and implantation site.

Biodegradability over desired timeframe with suitable mechanical properties and non-harmful degradation products.

Not containing harmful impurities.

A host response *in vivo* that does not prevent desired tissue development; i.e., inflammation and foreign-body response are not excessive.

Ability to be fabricated into desired structures.

Cost-effective.

Ability to be sterilized without harmful changes to their chemical or physical properties.

Adequate stability and shelf-life.

Ability to promote desired cellular responses, e.g., proliferation, differentiation, gene expression.

clinical acceptance, with very high costs and relatively low rates of translation from the laboratory to the clinic.⁵³ Despite this, much research continues and a range of such materials are in this testing pipeline.

Biomaterials for tissue engineering may be naturally occurring in the human body or derived from other natural or synthetic sources. They may be ceramics, polymers, hydrogels, or composites of these. Decellularized tissues are also used as biomaterials to support tissue growth. The physical form of biomaterials for tissue-engineering applications can also vary to suit the application – solid materials, porous scaffolds, microspheres, hydrogels, injectable materials that may cross-link *in situ*, or other configurations can be fabricated. Whilst it may be feasible to produce complex biomimetic materials to influence cell fate *ex vivo*, simplicity is also desirable to facilitate regulatory approval and translation of new materials into clinical application.⁵⁴ Selection of biomaterials will depend on the specific requirements of the tissue being targeted.

Biodegradable materials

Most biomaterials used in tissue engineering applications are biodegradable so that, over time, the material will disappear at a specified rate and be replaced by neotissue. The rate of degradation can vary widely so the mechanical integrity may be retained for as little as days or weeks, or as long as a year or more. The rate of degradation and loss of integrity will depend on the type of biomaterial, the site of implantation, properties of the biomaterial construct such as surface area to volume ratio, size, and surface chemistry. Fig. 16.6 shows examples of the loss of mechanical strength of biodegradable polymers.

As these materials degrade over time, one of the major challenges with biomaterial design is the prevention of sudden loss of physical integrity. Additionally, rapid degradation may lead to excessive concentrations of the degradation products of a biomaterial that can cause adverse tissue reactions. This

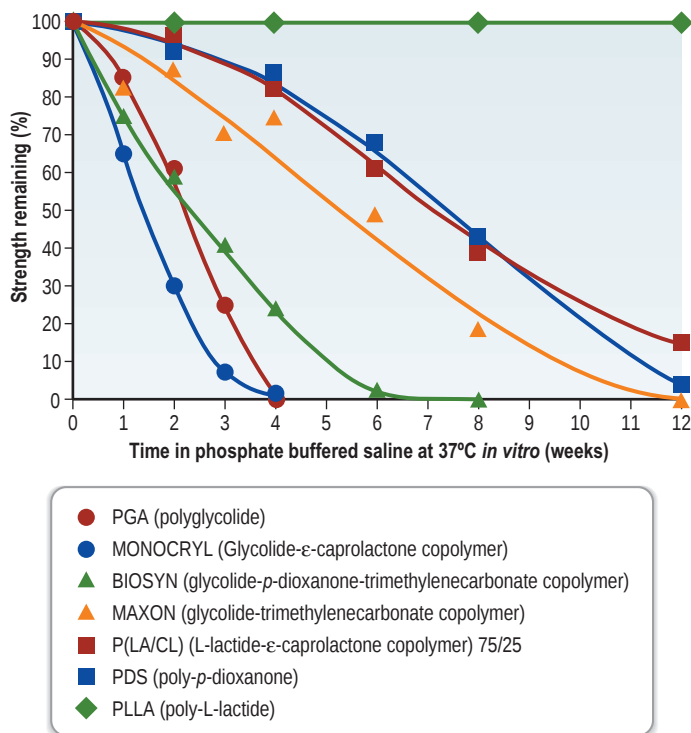


Fig. 16.6 Changes in tensile strength of biodegradable polymers during degradation *in vitro*. (Reproduced from Suzuki M, Ikada Y. *Biodegradable polymers in medicine*. In: Reis RL, Román JS (eds). *Biodegradable Systems in Tissue Engineering and Regenerative Medicine*. Boca Raton: CRC Press, 2005.)

is well known for the polylactides and polyglycolides that can undergo autocatalytic degradation with decreasing pH inside a thick-walled construct and “acid burst” leading to reduced local pH and tissue necrosis. For this reason, it is important to consider degradation rates and mechanisms in designing the composition and architecture of tissue-engineering constructs using biomaterials.

Natural biomaterials

Natural biomaterials may have the benefits of being chemically similar or identical to molecules in the body, readily degraded *in vivo*, and able to interact with cells on a molecular level. However, they can be difficult to obtain and purify, vary in properties between batches, may be difficult to sterilize, alter their properties during storage, and they may elicit significant immunogenic responses. Naturally derived biomaterials investigated for tissue engineering include proteins (e.g., collagen, gelatin, silk), polysaccharides (e.g., chitosan, hyaluronic acid), polynucleotides and extracts of ECM components.⁵⁵ These materials may be modified to tailor their properties, such as via chemical cross-linking to slow degradation and increase mechanical strength.

One natural biomaterial that is gaining increasing attention is decellularized extracellular matrix (dECM). During decellularization, cells are removed from allografts or xenografts to reduce immunogenicity but much of the complex composition and architecture of the ECM may be retained.⁵⁶ One limitation of synthetic materials is that they cannot contain the large number of biomolecules present in the ECM whilst the dECM has the potential for containing important factors, even

those that have not yet been identified. One interesting application of dECM is in the expansion of stem cells. Recently, MSCs have been cultured on dECM and the cells have illustrated significantly higher proliferation rates and maintenance of stem cell phenotype, clearly illustrating the importance of environmental control during cell culture conditions.⁵⁷

Polymeric biomaterials

Hydrophobic polymers

Numerous synthetic polymers are used in medicine and some of these are biodegradable (or bioresorbable) *in vivo*. Fig. 16.7 shows examples of the chemical structures of biodegradable polymers that could be used in tissue engineering. Among these, the polyesters poly(glycolic acid) (PGA), poly(lactic acid) (PLA) and poly(ε-caprolactone) (PCL) and their copolymers such as poly(lactide-co-glycolide) (PLGA) have been widely used in tissue-engineering approaches.⁵⁸ The mechanical strength and degradation rate of these polymers can be tuned over a wide range by changing the polymer properties (molecular weight, composition, molecular architecture, crystallinity, hydrophobicity).⁵⁹ However, many biodegradable synthetic polymers are quite hydrophobic, unlike the ECM. Exposure of such surfaces *in vivo* can lead to nonspecific adsorption of proteins of mixed orientation and states of denaturation, potentially resulting in a foreign-body reaction (FBR) to the material.⁶⁰

Hydrogels

Hydrogels are water-swollen cross-linked polymer networks which can absorb up to thousands of times their dry weight of water, which gives them the advantage of being more like most natural tissues and allowing mass transport to and from cells.⁶¹ They may be formed by physical (hydrogen bonds, ionic interactions, molecular entanglements, hydrophobic interactions) or chemical interactions (covalent bonds) and this affects their stability and degradation rates. The mechanical strength of hydrogels can be tuned within a limited range and their degradation tends to be faster than for other biomaterials. Hydrogels may be naturally derived (e.g., collagen, gelatin, hyaluronic acid, alginate) or synthetic (e.g., poly(ethylene glycol) (PEG)-based polymers).

Ceramic biomaterials

Ceramic biomaterials are primarily utilized in tissue engineering of hard tissues. Calcium phosphates, such as hydroxyapatite, and bioactive glasses have been developed as bioceramics for bone tissue engineering. Bioceramics are brittle but have high compressive strength, can bond strongly to bone, and can be osteoinductive.

Advanced biomaterials for tissue engineering

In the early days of tissue engineering, commodity materials were often used. However, these materials are often not suitable, as described above. Now we are in an exciting age of biomaterials science where materials are being designed to have tailored interactions with biology using our growing knowledge about how cells interact with their environments in order to lead to improved healing.⁶² Here we present an overview of some of these strategies and how they apply to tissue engineering.

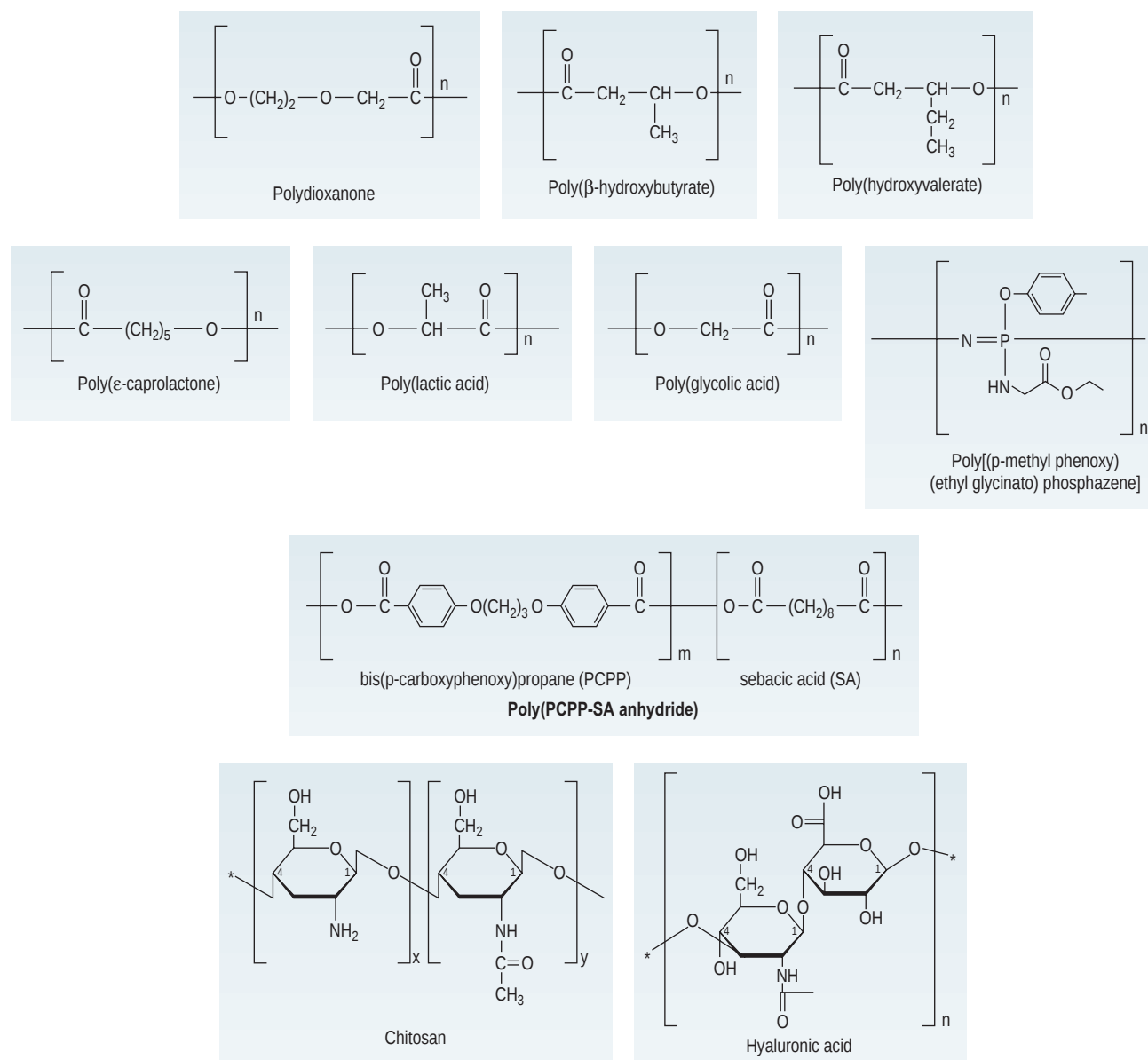


Fig. 16.7 Chemical structures of selected biodegradable polymers of potential interest in tissue engineering. (Reproduced from Kohn J, Abramson S, Langer R. *Bioresorbable and bioerodible materials*. In: Ratner BD, Hoffman AS, Schoen FJ, et al. (eds). *Biomaterials Science*. Amsterdam: Elsevier, 2004;115–217. Chitosan reproduced from Guibal E, Vincent T, Blondet FP. *Biopolymers as supports for heterogeneous catalysis: focus on chitosan, a promising aminopolysaccharide*. In: SenGupta AK (ed). *Ion Exchange and Solvent Extraction: A Series of Advances*. Boca Raton: Taylor & Francis; 151–292. Hyaluronic acid reproduced from Yannas IV. *Natural materials*. In: Ratner BD, et al (eds). *Biomaterials Science – An Introduction to Materials in Medicine*. Amsterdam: Elsevier; 2004.)

Tailored delivery systems

As discussed above, soluble bioactive molecules play a critical role in natural tissue morphogenesis and control of their delivery both spatially and temporally to growing tissue may significantly enhance tissue-engineering outcomes. Molecules such as growth factors, anti-inflammatory peptides, and drugs may be incorporated into biomaterial delivery vehicles for release at the desired time during tissue development.^{63–65} The release systems may be designed to deliver multiple molecules over different timescales via continuous or pulsatile delivery,⁶⁶ which may be programmed or triggered by some change in the local environment.⁶⁷ Delivery systems can be fabricated from biodegradable polymers in the form of micro- or nanoparticles or capsules, or incorporated into other

biomaterial constructs such as within the walls or on the surfaces of scaffolds or hydrogels.⁴⁷ It is critical to the design of an effective delivery system that the payload of bioactive molecules retains its conformation and bioactivity throughout the loading and release processes. An additional challenge is the prediction of release rates *in vivo*, which generally differ significantly from those *in vitro*.

Controlled delivery of growth factors is desirable as they have short half-lives *in vivo*, are relatively slow to diffuse due to their size, and may have undesired effects if delivered systemically.⁴⁶ The potential benefits of growth factor delivery on adipose tissue engineering were demonstrated *in vivo* using gelatin microspheres to deliver fibroblast growth factor-2 (FGF-2) over an extended time in a mouse tissue-engineering chamber.⁶⁸ Chambers containing an autologous

fat graft and gelatin microspheres loaded with FGF-2 grew significantly more tissue than controls with free FGF-2 or blank microspheres (Fig. 16.8).

Similar approaches are also being investigated for cell delivery, wherein cells may be loaded onto degradable microspheres *in vitro*, allowed to attach, migrate, and proliferate on or within the spheres and then delivered to a target site for tissue growth. This significantly increases the surface area available for attachment of adherent cells and using biodegradable beads that can be delivered *in vivo* avoids the need to detach the cells from the culture surface for delivery.⁶⁹ It has been shown that ASCs loaded into chitosan microspheres were viable and maintained their multipotency after *in vitro* culture.⁷⁰

Smart polymers

Changes in environmental conditions can result in changes to the molecular conformation of many materials. These environmentally-induced changes may be harnessed, resulting in so-called smart polymers (Fig. 16.9). These types of change can be used to encapsulate and release payloads of cells or drugs, to form gels upon injection *in vivo*, or for cell sheet engineering.^{60,71,72} A classic example of a smart polymer is the thermo-responsive polymer N-isopropylacrylamide (NIPAM) which is often used in tissue engineering applications. This material can be used to grow confluent cell sheets and then to detach the intact sheet along with the ECM that the cells have deposited.⁷³

Non-fouling materials

Another key challenge related to biomaterials is the foreign body response (FBR) seen *in vivo* with almost all synthetic biomaterials used clinically, be they polymers, ceramics, or hydrogels. Approaches to reduce the FBR to biomaterials *in vivo* may use physical properties, such as by creating spatial

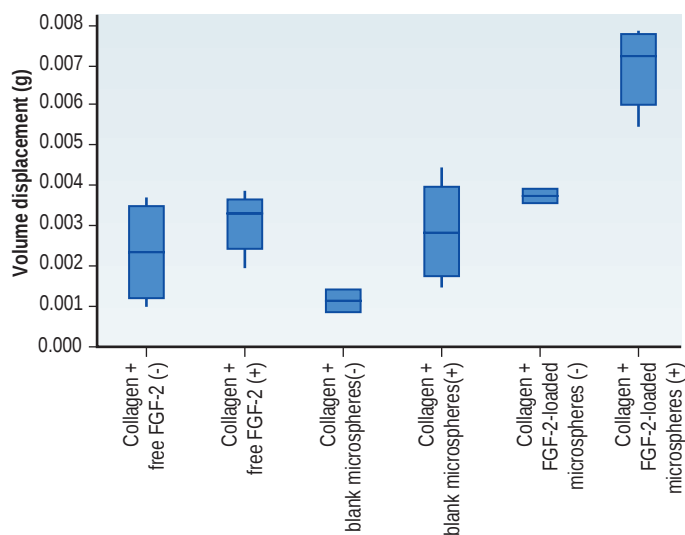


Fig. 16.8 Effect of controlled release of a growth factor on tissue development *in vivo*. Cross-linked gelatin microspheres suspended in collagen were used to deliver fibroblast growth factor-2 (FGF-2) in a tubular mouse tissue-engineering chamber enclosing superficial epigastric vessels in the groin of mice, with (+) or without (-) an autologous fat graft. (From Vashi AV, Abberton KM, Thomas GP, et al. *Adipose tissue engineering based on the controlled release of fibroblast growth factor-2 (FGF-2) in a collagen matrix*. Tissue Eng. 2006;12:3035–3043.)

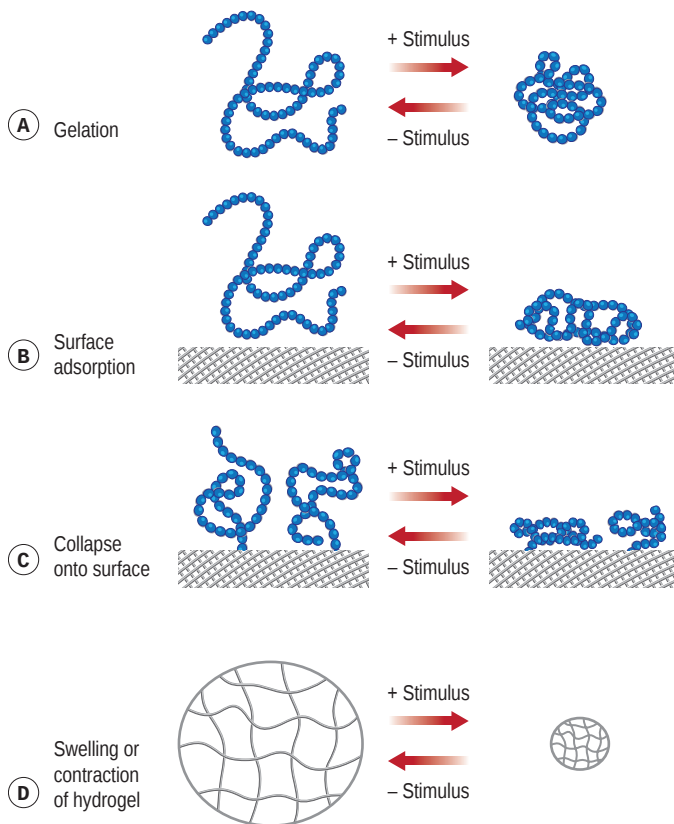


Fig. 16.9 Potential reversible responses of “smart polymers” to environmental stimuli. (A) Gelation. (B) Surface adsorption. (C) Collapse onto surface. (D) Swelling or contraction of hydrogel. (From Hoffman AS. *Applications of “smart polymers” as biomaterials*. In: Ratner BD, Hoffman AS, Schoen FJ, et al (eds). *Biomaterials Science*. Amsterdam: Elsevier, 2004;107–115.)

features that lead to reduced fibrosis (e.g., porous polymers with pores of around 30 μm ⁷⁴ or small-diameter fibers⁷⁵). Surface chemical properties can also be used to reduce the FBR to biomaterials, such as via attachment of oriented biomolecules.⁷⁶

One of the more successful strategies is the use of chemical surface modifications to create the so-called non-fouling surfaces. An initial stage of FBR is the adsorption of a complex layer of biomolecules from body fluids that can be denatured and lead to an immune reaction. Non-fouling materials (or stealth materials) resist the adsorption of these proteins. Usually these surface modifications make the material hydrophilic yet electrically neutral and the mechanism of action is believed to be that the surfaces hold their waters of hydration instead of allowing them to be displaced by adsorbing biomacromolecules. A myriad of strategies have been employed in order to generate non-fouling outer layers on biomaterials (e.g., by layer-by-layer assembly of polyelectrolytes ending with a nonadhesive outer layer,⁷⁷ or attachment of PEG^{15,78}). However, many strategies that show promise *in vitro* suffer from enzymatic attack and changes to the biomaterial surface *in vivo* during the acute inflammatory stages of the wound-healing response, and so their *in vivo* performance may be disappointing. Creating new generations of non-fouling materials with improved *in vivo* performance is an active area of research and includes candidates such as zwitterionic polymers, mixed charged polymers, and polyoxazolines.⁷⁹

Biofunctionalized materials

Cells will often attach to biomaterials implanted into the body, and this attachment is mediated by a layer of adsorbed proteins that contain cell binding sites. The abovementioned non-fouling technologies result in interfaces that do not adsorb proteins so are also resistant to cellular attachment. Such interfaces represent a “blank slate” for tissue engineers. These surfaces can then be decorated with bioactive molecules, usually through covalent immobilization. These biofunctionalized materials are then able to specifically interact with receptors on the cell surface and drive cellular behavior with biological specificity. The most common biofunctionalization strategy is to generate materials that contain ligands that engage specific integrin receptors. Thus, only cells that express the appropriate integrin are able to adhere to the material. The interaction of cells with such a surface depending on whether the surface has binding sites of suitable orientation and conformation to enable attachment of the cells, and the density of such sites. This in turn can affect cell morphology and migration rates (Fig. 16.10). Mostly these ligands are adhesion sites found in the native ECM (e.g., the RGD tri-peptide found in fibronectin),⁸⁰ but researchers have also performed analyses to discover unique receptors present on their cell type of choice. For example, a phage display library was screened in order to identify ligands specific to an outgrowth of endothelial progenitor cells but not other commonly occurring cell types. These ligands were then used to functionalize a biomaterial resulting in an interface inhabited exclusively by the target cell of interest.⁸¹

In addition to adhesion ligands, other bioactive molecules have been incorporated into synthetic materials in order to tailor biological interactions. For instance, the ECM acts to locally sequester growth factors, and similarly synthetic ECMs with tethered growth factors have been generated. Additionally, biofunctionalization has been used to tailor biomaterial degradation. The abovementioned biodegradable materials usually undergo some form of degradation reaction, for example hydrolysis of a chemical bond. This does result in a material that degrades; however, the degradation occurs regardless of cellular/tissue infiltration. However, cells move through the native matrix through secretion of matrix metalloproteinases that locally degrade the matrix. Advanced hydrogels that are crosslinked with peptide sites that are degraded by such metalloproteinases have been developed so that the biomaterial degradation rate adapts to the tissue growth rate.⁴⁸

Tissue engineering constructs

The abovementioned biomaterials are generally fabricated into a tissue scaffold to support regeneration. Usually, this

involves embedding cells within a hydrogel or incorporating microporous structures to enable cellular infiltration and metabolite diffusion. The design of biomaterial constructs for tissue engineering is complex and varies significantly depending on the tissue target. Even for specific tissue types, various design criteria may be considered (Box 16.2) and the definition of ideal designs is not yet well established.

Biomaterial constructs for tissue engineering can be fabricated into structures such as porous scaffolds and hydrogels, meshes or microspheres using a variety of techniques, including polymer phase separation, particle or foam templating, cryogelation, electrospinning and rapid prototyping methods like 3D-printing (discussed further in the emerging technologies

BOX 16.2 Key design criteria for tissue engineering scaffolds

Biomaterial selection, including:

- chemical composition
- molecular weight
- polydispersity
- crystallinity
- presence of any impurities (e.g., catalyst residues)

Internal 3D porous architecture:

- pore sizes
- pore shapes
- pore interconnectivity
- volume fraction of pores
- wall thicknesses

Surface chemistry

Surface topology

Degradation profile and products

Mechanical properties (initially and during degradation):

- elasticity
- strength
- toughness

Effects on cellular processes

In vivo effects (e.g., immune responses, foreign body reactions)

Ability to be fabricated reproducibly and economically

Ability to be sterilized without unacceptable property changes

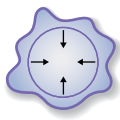
Intracellular contraction forces Substratum adhesive strength	Large	Intermediate	Small
Typical cell morphology			
Migration speed	Negligible	Significant	Negligible

Fig. 16.10 Effects of cell–substrate interactions on cell migration speed. (Reproduced from Palsson BO, Bhatia SN. Tissue Engineering. Upper Saddle River, NJ: Pearson Education; 2004.)

section).^{51,82–86} The techniques for tissue-engineering scaffold fabrication have been widely reviewed.^{53,87–90} A limited but growing range of biodegradable scaffolds are available commercially for cell culture and very specific approved clinical applications, examples of which are discussed in the case studies section at the end of this chapter.

Scaffolds of various internal architectures can be produced (Fig. 16.11) with different mechanical and degradation properties. The porosity must be interconnected and of sufficient size for molecular transport, cell migration, and vascularization. The size required may be larger than the minimum size

required to fit cells or blood capillaries. Cao *et al.* found that pores of at least 300 μm were needed for tissue survival in PLGA scaffolds where a significant FBR occurred inside the scaffolds.⁹¹

Ideally the mechanical strength of tissue-engineering constructs is matched to that of the target tissue to favor the desired cellular behavior, as discussed above, and ensure the construct will not collapse under the forces applied *in vivo* but will also not cause stress shielding to the surrounding tissue, which can lead to changes such as bone resorption. The construct should maintain its strength during tissue development

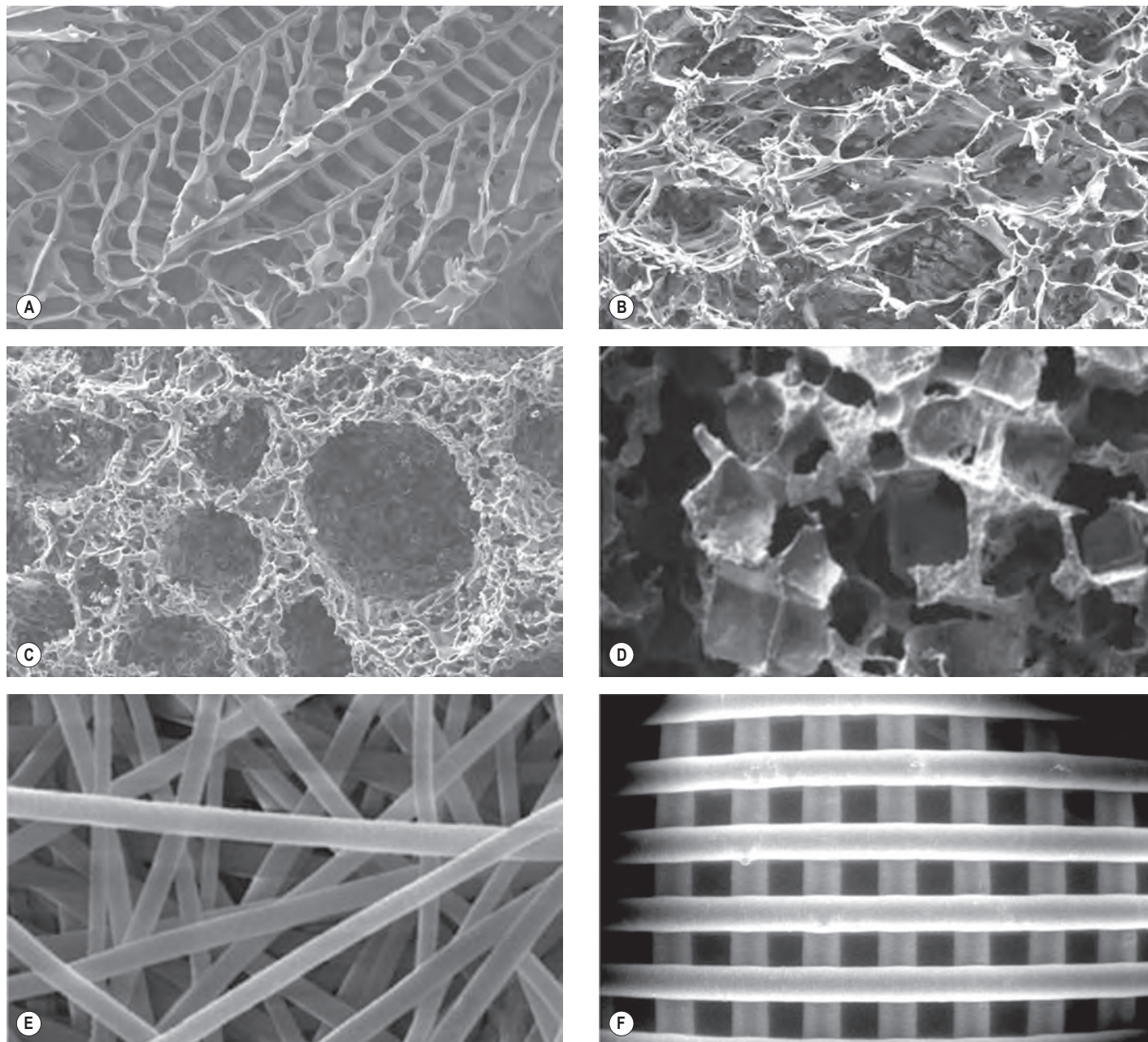


Fig. 16.11 Scaffold morphologies produced by thermally induced phase separation (A–C). (D) Particulate leaching. (E) Electrospinning. (F) Rapid prototyping. (A–C, Reproduced from Cao Y, Croll T, Cooper-White JJ, et al. Production and surface modification of polylactide-based polymeric scaffolds for soft tissue engineering. In: Hollander AP, Hatton PV (eds). *Biopolymer Methods in Tissue Engineering*. Totowa, NJ: Humana Press; 2004:87–112. (D–E) Reproduced from Kretlow JD, Mikos AG. From material to tissue: biomaterial development, scaffold fabrication, and tissue engineering. *AIChE J*. 2008;54:3048–3067. (F) Reproduced from Shor L, Gucer S, Chang R, et al. Precision extruding deposition (PED) fabrication of polycaprolactone (PCL) scaffolds for bone tissue engineering. *Biofabrication*. 2009;1:1–10.)

until the newly formed tissue can withstand the mechanical forces at play.⁹² Scaffold mechanics can be varied by adjusting the scaffold material, fabrication process, porosity (pore size, volume and architecture), grain size (for ceramics) and using composites such as nanoparticles of hydroxyapatite in a polymer matrix, as well as nanoparticle surface patterning.^{93,94} The effect of porosity in ceramics is illustrated in Fig. 16.12. Ceramics are prone to brittle failure and purely ceramic scaffolds with the porosity desired for effective vascularization may not have sufficient strength and toughness for load-bearing bone tissue engineering, which limits their clinical application.⁹⁵

Fabrication processes can incorporate viable cells and/or bioactive molecules with biomaterials by suitably gentle processes and scaffold-free construct production methods are also being developed, such as by using magnetic fields to arrange cells.⁹⁶

Vascularization in tissue engineering

The remarkable advances in tissue engineering during recent years have highlighted the importance of vascularization as it has become clear that survival, growth and function of an engineered construct are highly dependent on an adequate and timely blood supply. Generally, cells do not survive beyond 150 μm from a capillary,^{6,97} although certain cells and tissues vary in their oxygen needs. As stated earlier, whilst the first attempts of tissue fabrication were focused mainly on tissues of either low oxygen requirements, such as cartilage and tendon, or very small thickness, such as skin, able to survive by diffusion, it is now widely accepted that the fabrication of thicker and more “oxygen-demanding” surrogates cannot be conceived without first addressing the issue of vascularization, currently one of the major hurdles in translating laboratory-based tissue engineering products into human practice.

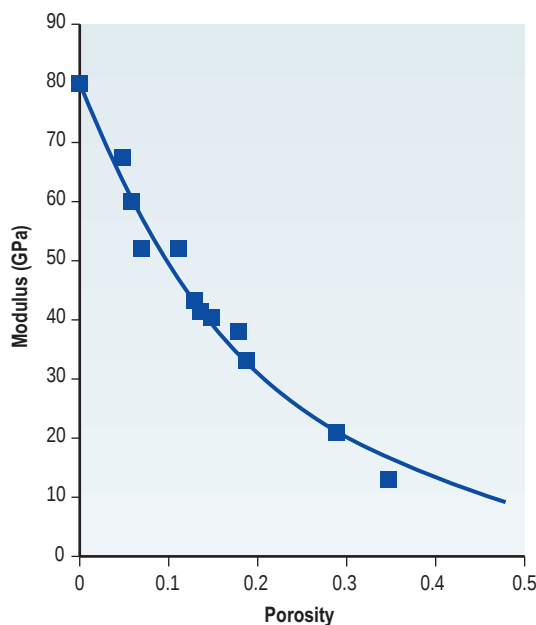


Fig. 16.12 Ceramic scaffold mechanical properties as a function of porosity. (From Boccaccini AR. *Ceramics*. In: Hench JRJ (ed.) *Biomaterials, Artificial Organs and Tissue Engineering*. Cambridge: Woodhead; 2005.)

Vasculogenesis, angiogenesis and inosculation

Understanding how the human vasculature develops, expands and connects to a grafted tissue is fundamental to successfully building a capillary network *in vitro* that is able to link to host's capillaries *in vivo* and ultimately support the growth, expansion and function of a tissue-engineered construct. *Vasculogenesis* refers to the development of new blood vessels from progenitor stem cells.⁹⁸ In the embryo, mesoderm cells are stimulated by FGF-2 to form hemangioblasts, a common precursor for vessel and blood cell formation. After pooling together into blood islands, hemangioblasts located at the periphery differentiate first into angioblasts and then into endothelial cells, which start to coalesce resulting in a primary vascular plexus.⁹⁹ Though initially it was assumed that vasculogenesis was exclusive to the embryological period, we know now that it also takes place in adult life driven by bone marrow-derived endothelial progenitor cells.¹⁰⁰ *Angiogenesis* describes the sprouting of blood vessels from pre-existing ones. Briefly, in this process endothelial cells respond to an angiogenic signal and increase vascular permeability allowing the extravasation of plasma proteins that form a transient matrix. A tip cell then migrates out of the vessel into the previously deposited matrix and leads the sprouting followed by stalk cells, which form a lumen. Once neighboring sprouts fuse, the neovessel becomes perfused and is further stabilized by the recruitment of pericytes and basement membrane restitution.¹⁰¹ *Inosculation* describes the process by which capillaries from a grafted tissue connect to those of the wound bed where it is applied. The exact mechanism by which such connection occurs and whether it is dependent on the characteristics of the grafted tissue are not entirely clear.^{102,103} What is clear, though, is that because it takes several days to ensue, inosculation is one of the limiting factors affecting prompt perfusion of a tissue-engineered construct.^{104–107} Such a period of time is too long to expect anything but very thin tissues to survive the transplantation anoxia. Nevertheless, some studies have achieved faster inosculation by using either fibroblasts or FGF-2, giving some interesting insights on how to accelerate the process and eventually make it clinically feasible.^{108,109}

Elements and strategies of vascularization in tissue engineering

As stated before, engineering of any 3D tissue or organ is highly dependent on an adequate blood supply. This can be achieved by either an extrinsic or an intrinsic approach. The extrinsic approach implies the direct implantation of a seeded scaffold that is gradually invaded by the host's vasculature, meanwhile relying solely on diffusion for survival. Alternatively, through a process named pre-vascularization, a capillary bed can be fabricated *in vitro* and then implanted *in vivo* where it will become perfused by inosculation rather than by capillary invasion (Fig. 16.13). In the intrinsic approach the organism is used as a bioreactor so that capillary sprouting occurs either before or concomitantly with cell differentiation and tissue growth.¹¹⁰ But before going into the detail of each of these approaches, one must first be familiarized with the different basic elements common to both strategies, which, similar to tissue engineering itself, are: cells, scaffolds and growth factors.

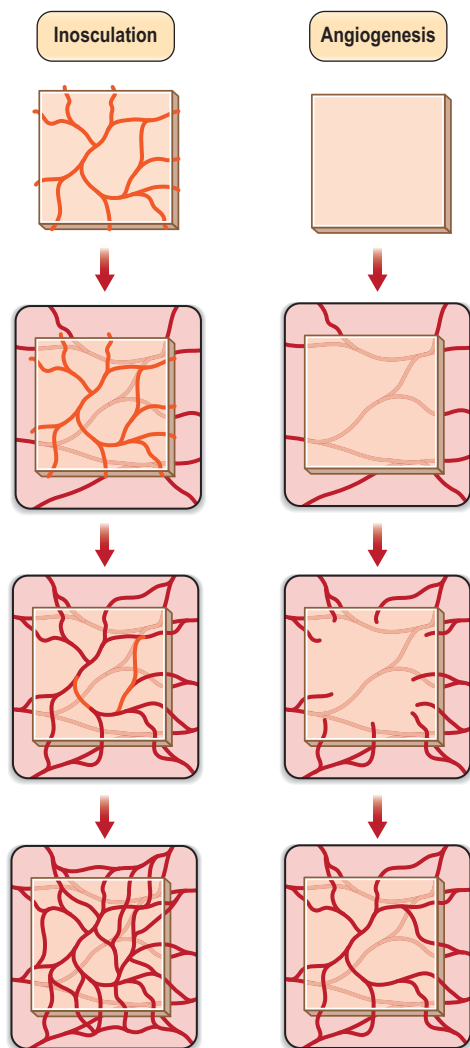


Fig. 16.13 Schematic illustration of the vascularization of a grafted tissue by inosculation and capillary invasion (angiogenesis). When a vascular network is fabricated prior to implantation, inosculation between the scaffold's vessels and bed capillaries at the periphery of the construct provides blood supply to the entire block. Conversely, if the scaffold is implanted without a pre-formed vascular network, adequate blood supply is only provided once host capillaries have completely invaded the construct.

Elements

Cells

A number of different cell sources have been trialed with varying degrees of success. In general terms, the vast majority of experiments attempting to build a capillary network use two cell lines, namely endothelial cells and supportive cells (Table 16.2). The logic in this is to try to mimic to some extent the processes of vasculogenesis and angiogenesis in which the lumen is formed by the endothelial cells while the stabilization and maturation of the newly formed vessels is partly the result of the structural and paracrine action of the perivascular supportive cells.

As can be seen in Table 16.2, there are a number of possible combinations. Whatever mixture is chosen, most of the latest research points towards better results obtained with bi-culture or even tri-culture compared with seeding endothelial cells alone.^{104,108,111,112} Additionally, it is interesting to note the fact

that adipose-derived stem cells have been used both as supportive and endothelial cells,^{113–115} with one study actually suggesting that ASCs alone may suffice for the formation of vascular lumina upon implantation.¹¹³ Of note also is the role of fibroblasts. As mentioned earlier, experiments using high concentrations of these cells have reported accelerated inosculation as early as one day post-implantation.¹⁰⁸ A further cellular element that has been explored with success in pre-vascularization is the stromal vascular fraction (SVF) from lipoaspirates. The presence of endothelial progenitors within the SVF cell population, as well as its remarkable proangiogenic potential, was reported more than a decade ago.^{116,117} More recently, other studies have reported on the successful growth of a functional capillary bed using SVF only.^{103,118} The current knowledge on the different components of SVF, namely mesenchymal stem cells, endothelial cells, endothelial precursors, vascular smooth muscle cells, pericytes and angiogenic growth factors make this lipoaspirate-derived cocktail a very reasonable and attractive source of the cellular elements needed to build a capillary network.^{119,120}

Scaffolds

The characteristics of scaffolds for tissue engineering have been described above. For vascularization, several of these matrices have been tested, all having their inherent pros and cons. Natural scaffolds include collagen, fibrin, starch, Matrigel®, decellularized matrix and silk fibrin. Synthetic materials on the other hand comprise mainly polyethylene glycol, poly (lactic glycolic) acid and polyurethane.¹²¹ Furthermore, clinically approved dermal substitutes such as Integra® and Matriderm® have also been used for prevascularization purposes by seeding them with endothelial colony forming cells (ECFCs) in association with either human dermal fibroblasts (hDFs) or bone marrow-derived mesenchymal stem cells (BMSCs).¹²² Whatever scaffold is used, it is important to consider the close cell–cell and cell–matrix interactions as well as the mechanical features that eventually guide and stabilize the newly formed vessels.¹²³ Likewise, since vasculogenesis and angiogenesis are deeply influenced by the presence of an

Table 16.2 Cells most commonly used for building capillary networks.

Endothelial cells (ECs)	Supportive cells
Human umbilical vein ECs (HUVEC)	Smooth muscle cells
Human dermal microvascular ECs (HDMEC)	Pericytes
Human endothelial colony-forming cells	Fibroblasts
Human iPS-derived endothelial precursor cells	Bone marrow MSC
Adipose-derived stem cells	Adipose-derived stem cells
Blood-derived endothelial progenitor cells	Human embryonic stem cells – MC
Adipose-derived endothelial progenitor cells	Human iPS – mesenchymal precursor cells
Bovine pulmonary artery ECs	10 T1/2 embryonic murine mesenchymal stem cells
Rat aortic ECs	

iPS, induced pluripotent stem cells; MSC, mesenchymal stem cells; MC, mesenchymal cells.

adequate extracellular matrix (ECM), it is equally important that the turnover between scaffold degradation and new ECM deposition by the cells occurs at a rate that neither impedes the growth of the network by being too slow, nor renders the construct unstable by being too fast.¹²¹

Growth factors

A complete and detailed explanation of the growth factors and signaling pathways involved in the process of angiogenesis is beyond the scope of this chapter. Herein, a general overview of the main growth factors that participate in the formation and sprouting of new blood vessels is presented.

Vascular endothelial growth factor A (VEGF-A) is the most important growth factor involved in angiogenesis in both health and disease,¹²⁴ acting mainly by binding to VEGF receptor 1 (VEGFR-1) expressed in endothelial cells, hematopoietic stem cells and inflammatory cells, and VEGFR-2, which is expressed mainly in endothelial cells. Additionally, neuropilins 1 and 2 (NRP1 and NRP2) are VEGF-A co-receptors, which can act either promoting VEGFR-2 activity or independently.¹⁰¹ Interestingly, the effect of VEGF-A on the developing vasculature is dependent on its isoforms and the way it is delivered. Thus, while soluble isoforms promote vessel enlargement, matrix-bound isoforms stimulate branching.¹⁰¹ Likewise, paracrine VEGF-A released by tumor, myeloid or other stromal cells increases vessel branching and renders tumor vessels abnormal retarding its progression,¹²⁵ whereas autocrine VEGF-A, released by endothelial cells, maintains vascular homeostasis.¹²⁶ As important as it is in the organism, VEGF-A has also been suggested to play a critical role in the design of clinically relevant tissue regeneration graft substitutes through its angiogenic effects and ability to chemoattract mesenchymal stem cells.¹²⁷

The fibroblast growth factor (FGF) family comprises 18 members that regulate a number of biological and developmental processes.¹²⁸ FGF-2 (also known as basic fibroblast growth factor, bFGF) is the one mostly involved in angiogenesis and is produced by a number of differentiated cells such as keratinocytes, mast cells, fibroblasts, endothelial cells and smooth muscle cells,¹²⁹ as well as by adult mesenchymal stem cells derived from bone marrow, adipose, and dermal tissue.¹³⁰ FGF-2 has been shown to exert a number of important actions related to neovessel formation such as stimulating migration and proliferation of endothelial cells *in vivo* and encouraging mitogenesis of smooth muscle cells and fibroblasts, which induces the development of large collateral vessels with adventitia.^{131,132} FGF-2 has been used with success in the prevascularization of scaffolds, with one study showing faster inosculation of the scaffold *in vivo* when this factor was added.¹⁰⁹

Platelet-derived growth factor (PDGF) and in particular PDGF-B released by endothelial cells also participate in the angiogenesis process mainly by attracting pericytes that will subsequently provide stability and structural support to the newly formed vessel.^{133,134}

Other proangiogenic factors identified are placenta-derived growth factor (PlGF), hepatocyte growth factor (HGF) and insulin growth factor 1 (IGF). Whilst these factors may play important roles in developmental and adult angiogenesis, for prevascularization purposes, it is likely that their role can be replaced by some of the other agents listed earlier, given the redundancy of factors and their functions.

Strategies

Extrinsic vascularization model of tissue engineering

The model of extrinsic vascularization relies on diffusion immediately after implantation until vascularization invades the construct from the periphery through into its core, a process that can take several days or weeks to be fully established. This model was the traditional prototype for 3D tissue engineering from its inception; nevertheless, it has become somewhat obsolete due to the growing knowledge on the importance of an adequate and prompt blood supply. Nowadays, it is mostly conceded that reliance on a 3D prefabricated structure to survive implantation by the random invasion of capillaries from the implantation bed is unlikely to be a viable concept, especially for tissues sizeable enough to be clinically useful. It may, however, still have a role in the engineering of thin or avascular tissues such as skin or cartilage. A number of animal models exploiting the extrinsic principle have been described (Box 16.3).

Interestingly, some studies have suggested that vasculogenesis in the subcutaneous model requires a significantly higher number of cells and growth factors compared with the brain, a fact that highlights the importance of implanting the scaffold in a well-vascularized environment to optimize perfusion.¹¹² To try to speed up the process, a number of modifications have been trialed to facilitate rapid vascularization upon implantation, including angiogenic growth factors,^{127,135} endothelial cells and MSC co-culturing for their angiogenic and paracrine effects,^{136,137} patterning of synthetic or collagen matrices with artificial vascular channels,^{138–141} bioactive scaffolds containing growth factors for controlled release,^{142–145} or decellularized whole-organ tissues that retain a skeletonized vascular tree which may be seeded with endothelial cells *ex vivo* or spontaneously endothelialized *in vivo*.¹⁴⁶ Additionally, cells may be subjected to ischemic preconditioning prior to seeding *in vivo* to tolerate the new environment better.^{5,147,148} Alternatively, current research is focusing on prevascularization, in which a capillary bed is built *in vitro* prior to implantation using a combination of the elements described previously. Once implanted, the capillaries on the periphery of the construct must inosculate with the recipient's vasculature to deliver oxygen and nutrients to the entire block (see Fig. 16.13). This approach, although not immediate, is seemingly faster and more reliable than waiting for the host's capillaries to invade the whole tissue from the periphery to its core, but still does not solve the issue of transient ischemia, which is not tolerated by a number of tissues. Even though some studies have achieved a significantly faster inosculation between 1 to 4 days,^{108,109,149} further research is still needed to establish this model of extrinsic vascularization as a feasible strategy for the engineering of sizeable 3D tissues. Finally,

BOX 16.3 Animal models for extrinsic vascularization in tissue engineering

Subcutaneous implantation

Subcutaneous implantation in polydimethylsiloxane wells¹⁰⁷

Dorsal skinfold chamber³³⁵

Cranial window³³⁵

despite the remarkable advances in the area of prevascularization that make us believe that the creation of thick, clinically relevant organs or tissues is within reasonable reach, there is yet an important hurdle to overcome, namely the fact that the vast majority of experiments are performed in healthy animals under relatively controlled conditions in comparison to the clinical scenario. In the latter, patients with damaged and scarred tissues, medical comorbidities, tobacco use and other adverse conditions are the substrate into which these prevascularized scaffolds will be eventually applied and expected to survive.

Intrinsic vascularization models and *in vivo* bioreactors

Prefabrication of flaps, where a blood vessel pedicle is implanted into living tissues to vascularize a dedicated territory such as skin,^{150,151} or prelamination, where several tissues are grafted around the pedicle so that they can be subsequently transferred as a composite tissue graft,¹⁵² has given tissue engineers insights into the importance of blood supply and how such vascularization might be incorporated into tissue-engineered products grown in the body.¹⁵³ This process involves the establishment of an intrinsic vascularization that grows in tandem with the tissue-engineered product and nourishes it progressively. When a vascular pedicle or loop is tunneled into a tissue plane, the surgical trauma, inflammation, and hypoxia stimulate release of proangiogenic growth factors and promote angiogenic sprouting, which links to the pre-existing vasculature (Fig. 16.14). We have exploited this concept for tissue engineering in a rat model, where a vessel loop is directed into a protected space that cannot collapse, such as a chamber box (Figs. 16.15–16.18).¹⁵⁴ The vessel loop sprouts new capillaries due to continuing ischemia within the chamber and shear forces in the loop further promote angiogenesis. The “wound” cannot contract or shut down, prolonging the ischemic stimulus, and altered mechanical forces and fluid shifts influence cell migration and proliferation within the chamber. The inflammatory environment of the chamber attracts neighboring and distant cells to participate in this frustrated repair process in an attempt to close the dead space, which is progressively replaced with new vascularized predominantly fibroblastic tissue (see Fig. 16.18). As the tissue grows, the angiogenic front moves centripetally and corresponds to the retreating zone of ischemia.¹⁵⁵ Tissue growth is enhanced when a collagen matrix is included in the chamber and the angiogenic tissue will readily accept a skin graft, thereby creating a vascularized flap. The angiogenic stimulus continues for at least 20 weeks but is maximal between 7 and 10 days (Fig. 16.19).¹⁵⁶ Simcock *et al.*³⁸ injected human angioblasts intravenously into rats with an arteriovenous loop chamber and observed that they could home to the chamber site. This was enhanced by SDF-1 delivery directly into the chamber and implies that vasculogenesis plays a role in the vascularization process (Fig. 16.20). The contribution of vasculogenesis to skin graft and flap healing has been elegantly investigated by Capla *et al.*¹⁵⁷ If fibroblasts are added to the chamber at the time of creation of the loop they survive and can proliferate.¹⁵⁸ We have developed a similar model of tissue engineering in the mouse using a “flowthrough” epigastric artery and vein in the groin surrounded by a sealed silicone tube, which includes Matrigel® matrix, a mouse sarcoma extract composed largely of laminin, and FGF,¹⁵⁹ which has also been described

by Walton *et al.*¹⁶⁰ (Figs. 16.21 & 16.22). We have studied the mechanism of angiogenic invasion into Matrigel®, as has been done also by Tigges *et al.* in mice.¹⁶¹ This highlights the pre-eminent role of bone marrow-derived macrophages and pericytes. Macrophages burrow into the matrix, creating channels which are lined initially by pericytes. Only later do endothelial cells follow and line the hollow tubes. Vessel-like networks form initially without any endothelial cell contribution but these cannot form without macrophages. This elegant exposé of the process of vascularization was specific to Matrigel® and may not necessarily reflect the vascularization process of wounds comprising other matrices. This intrinsic system of vascularization can support seeded cells and the histological pattern of their survival clearly demonstrates the intimate role of the neovasculature in nourishing the cells. Fibroblasts¹⁵⁸ as well as specialized cells including neonatal cardiomyocytes¹⁶² (Fig. 16.23), islet cells,¹⁶³ and myoblasts⁵ survived in the chambers but quantification of survival is difficult and almost certainly many cells apoptose. Delayed seeding of cells into a prevascularized chamber enhances cell survival in the rat⁵ and mouse chambers.¹⁶³ When ASCs were implanted into the mouse chamber model in Matrigel® and traced by sex mismatching or human to animal stains, new fat tissue formed but the stem cells were found to contribute only to new blood vessel formation. New fat was of host origin, indicating that the stem cells did not differentiate into fat but were inductive for endogenous fat formation. It is well recognized that MSCs have paracrine effects, including angiogenesis, cell recruitment, homing, anti-inflammatory, and antiapoptotic effects.¹⁶⁴ We have compared survival of liver precursor cells cultured on 2D plastic delivered as cell suspensions with 3D gel-cultured spheroids.¹⁶⁵ In the spheroid form greater numbers of cells implant and survive in the chamber, suggesting that survival is related to other factors such as cell–cell microenvironment apart from pure vascularization. When solid tissue pieces such as muscle were implanted into the chamber they did not survive but regularly the dead tissue induced endogenous fat replacement.¹⁶⁶

Khouri *et al.*¹⁶⁷ designed a tissue-engineering chamber (BRAVA®) to induce fat growth for breast tissue replacement. It consists of a suction device applied to the external surface of the breast which, when worn regularly for prolonged periods, pulls the tissue away from the chest wall, creating tissue injury, inflammation, and a potential space. These are the key elements of our tissue engineering chamber where inflammatory cytokines stimulate angiogenesis and attract stem cells while the vacuum creates the space. Biomechanical forces including fluid shifts also influence cell behavior. Subsequently, Khouri included massive volumes of fat injection which are seen to survive most probably thanks to the well-vascularized environment generated by the previously applied suction.^{168,169} This modification is akin to our model of seeding cells into a preconditioned prevascularized chamber. In another original concept of intrinsic vascularization for tissue engineering using “autologous microcirculatory beds”, Chang *et al.*¹⁷⁰ devised an *ex vivo* perfusion chamber where an explanted flap of tissue, which is in essence a preformed vascular bed, can be continuously perfused with oxygen-carrying nutrient fluids for periods of up to 24 hours through its vascular pedicle. During this time, the flap was infused with cells intravascularly, including stem cells, which egressed from the microcirculation into the tissues to form cell

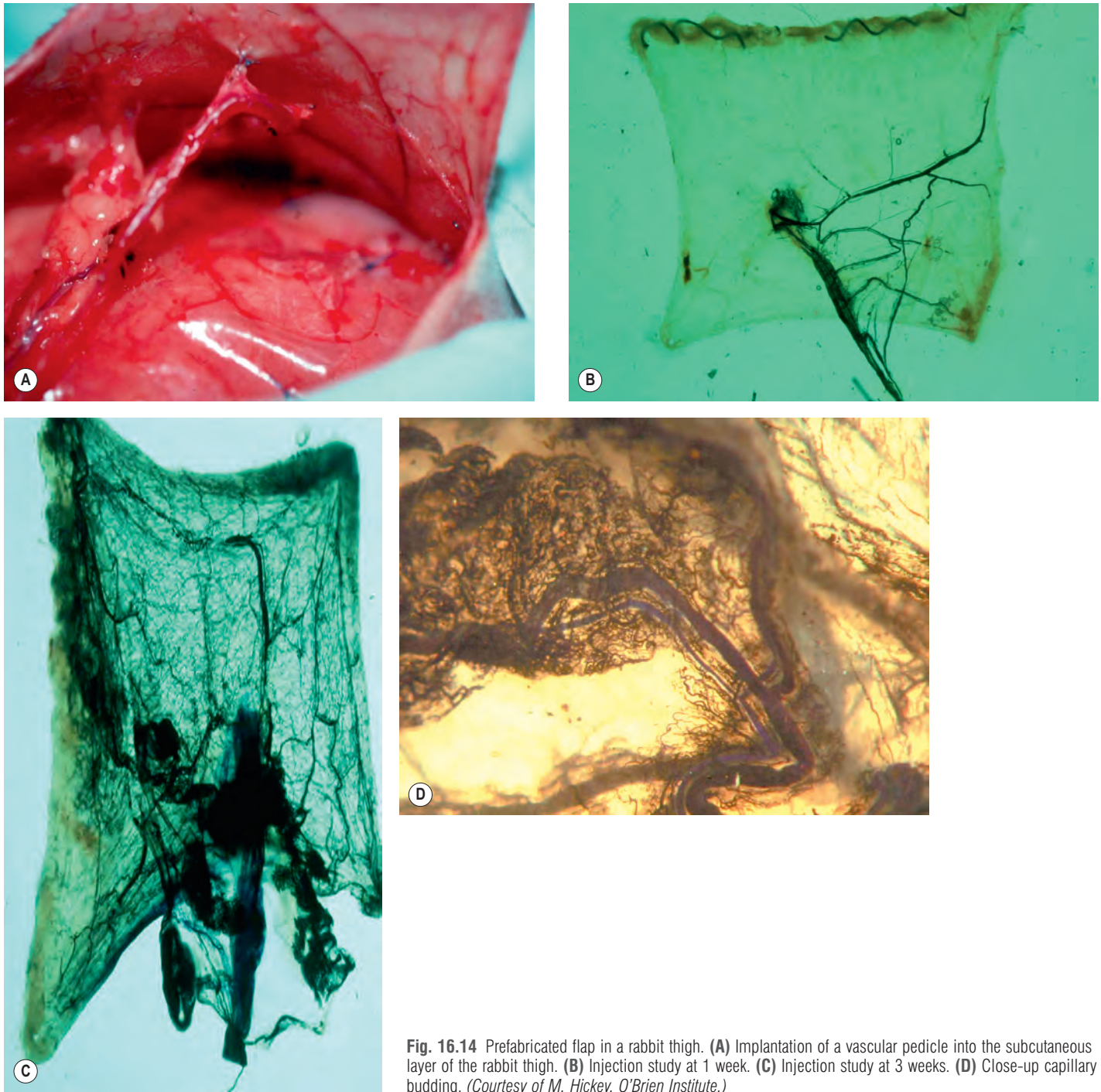


Fig. 16.14 Prefabricated flap in a rabbit thigh. (A) Implantation of a vascular pedicle into the subcutaneous layer of the rabbit thigh. (B) Injection study at 1 week. (C) Injection study at 3 weeks. (D) Close-up capillary budding. (Courtesy of M. Hickey, O'Brien Institute.)

clusters. The flap was then reimplanted by microvascular anastomosis into the animal. Similarly, Sekine *et al.*¹⁷¹ have also harvested a capillary bed using a piece of rat femoral muscle tissue attached to the femoral artery and vein. After connecting it to a bioreactor and perfusing it, the authors placed cell sheets containing cardiac and endothelial cells and demonstrated functional connections between the sheet and the bed. These authors also found that the co-culture of endothelial and cardiac cells as well as the addition of FGF-2 led to a more robust vascularization of the tissue in the bioreactor. Finally, they were able to transplant the whole construct back into the rat as a microsurgical free flap using the carotid artery

and jugular vein as recipient vessels. This model points to a new direction in organ regeneration or cell transfection to deliver deficient proteins. Furthermore, it is indeed attractive in the sense that it circumvents the need to “artificially” create a vascular network and ensures immediate vascularization after pedicle anastomosis without having to rely on invasion or inosculation. Moreover, at a first glance this method seems applicable to soft tissue reconstruction by harvesting a pedicle with a small amount of tissue which is expanded *in vitro* and transplanted back into the patient; however, it unfortunately still involves the sacrifice of a vascular pedicle with its inherent donor site morbidity.



Fig. 16.15 Polycarbonate chamber (left) comprising a base plate and a lid (right).

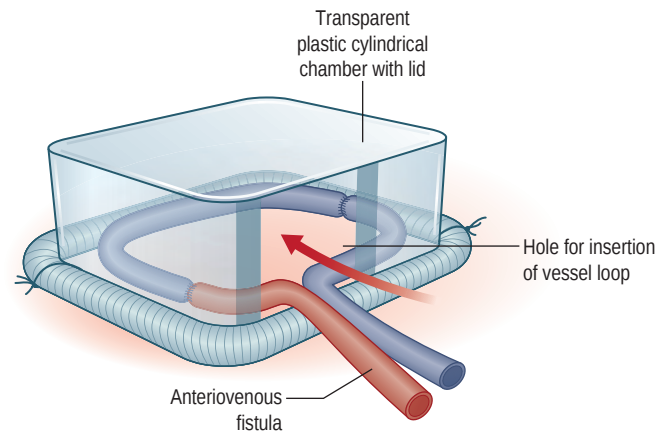


Fig. 16.16 Chamber box with arteriovenous loop.

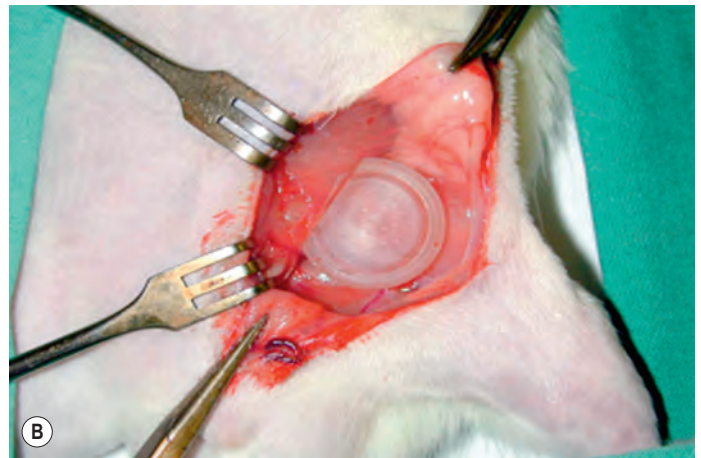
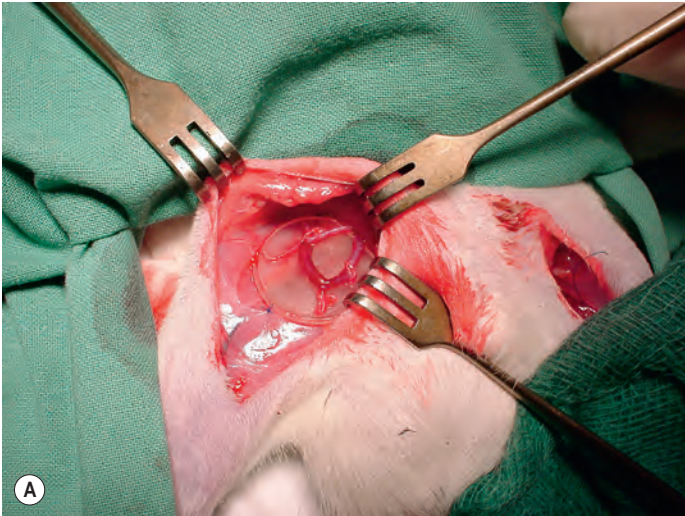


Fig. 16.17 Chamber implanted (A) in rat groin, where (B) it is closed and buried.

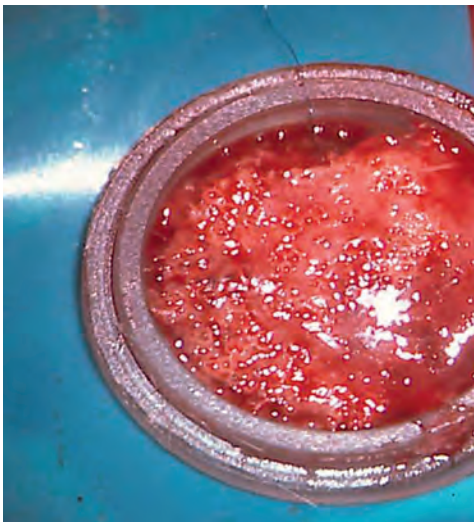


Fig. 16.18 Chamber opened after 6 weeks showing tissue formation.

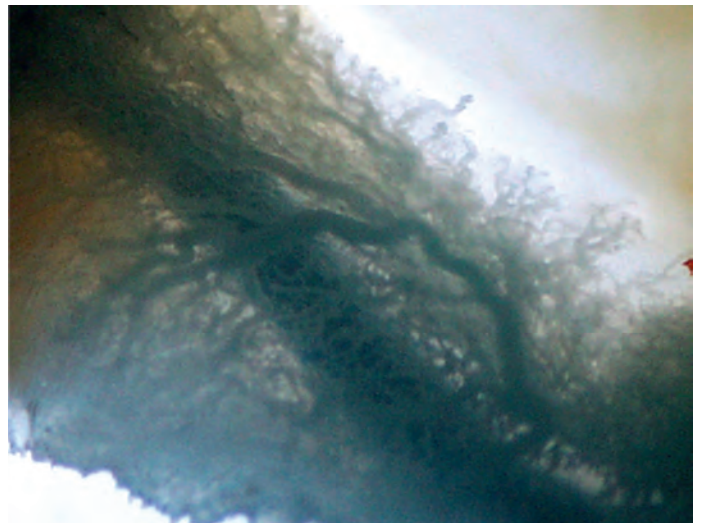


Fig. 16.19 Angiogenic sprouting from the vessel loop at 10 days. (Courtesy of Dr. Z. Lokmic.)

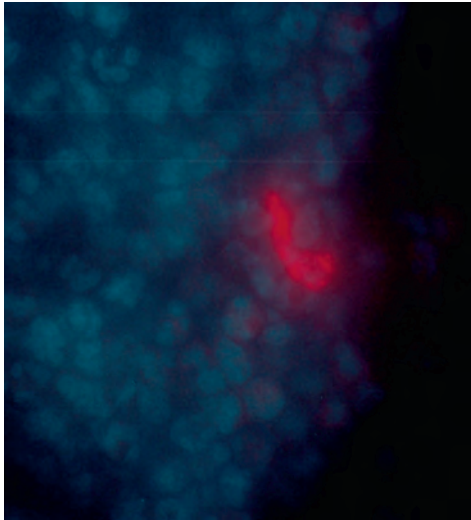


Fig. 16.20 Human angioblast, Dil-labeled, homing to the rat chamber after intravenous injection. (Courtesy of J. Simcock and G. Mitchell, O'Brien Institute.)

In a different model of intrinsic 3D tissue engineering, a vascularized flap of fat tissue, when implanted into an empty chamber space, will expand and attempt to fill the space. We initially observed in our mouse Matrigel® model that if a fat pad was used to plug one end of the chamber tube and wax the other, fat gradually replaced the Matrigel® by direct extension from the pad.¹⁵⁹ When we placed an isolated fat pad on a vascular pedicle into the chamber in a rat even without matrix, the fat tissue expanded. When perforations were included in the chamber shell the space completely filled with tissue, approximately 40% of which was new fat.¹⁷² This result was repeated in a pig model which grew over 50 mL of new fat (Fig. 16.24).¹⁷³ Although surgical trauma, ischemia, and inflammation play a role through biochemical signaling in this new tissue growth, it is likely that the tissue flap finding itself in an empty space reacts to the changed biomechanical

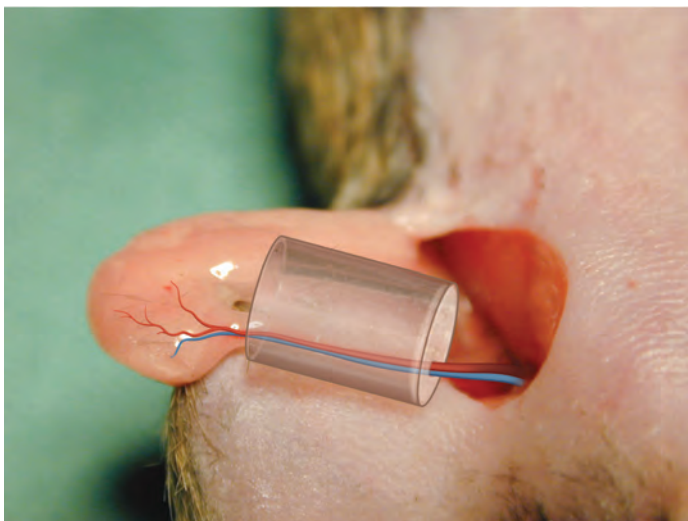


Fig. 16.21 Tissue-engineering silicone tube chamber in a mouse. (Reproduced from Cronin KJ, Messina A, Knight KR, et al. *New murine model of spontaneous autologous tissue engineering, combining an arteriovenous pedicle with matrix materials*. *Plast Reconstr Surg*. 2004;113:260–269.)



Fig. 16.22 Vascularization into the Matrigel® in a mouse chamber at 4 weeks.

environment through focal adhesion transmembrane pathways as discussed earlier,⁴¹ stimulating cell migration and growth. However, quantification of this effect is difficult *in vivo* and the precise process remains unclear.

Encouraged by the promising findings in animals, we questioned whether the tissue-engineering chamber might have a similar effect in the clinical setting and thus we scaled up our research into a human trial.¹⁷⁴ Five patients were recruited, all candidates for breast reconstruction who wished to avoid breast implants if possible and were unsuitable for autologous reconstruction. A pedicled fat flap based on the thoracodorsal system ranging from approximately 5 to 50 mL was harvested, transposed onto the chest wall and placed inside a perforated, acrylic, custom-made chamber ranging from 180 to 360 mL. Magnetic resonance imaging was performed every three months and the chambers removed six months after implantation. One patient was withdrawn from the trial at 7 weeks due to painful rubbing of the chamber's rim on her ribs. In another patient there was significant expansion of the flap by 6 months on MRI and it was mutually agreed to leave the chamber *in situ* for twelve months total. At exploration the whole chamber space had filled with fibrofatty tissue surrounded by a fibrous capsule representing an

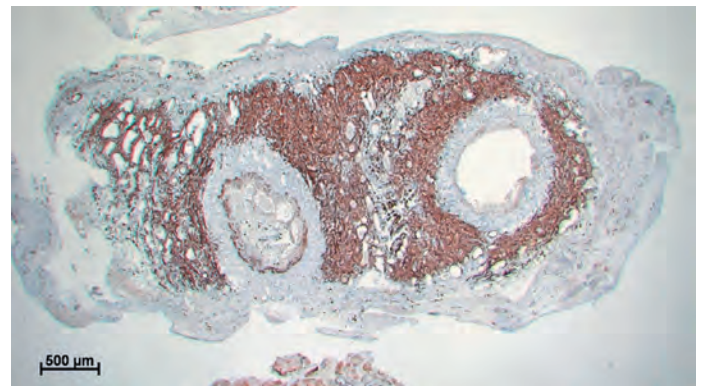


Fig. 16.23 Neonatal cardiomyocytes seeded into rat chamber showing maximum survival around the vessel loop. (Courtesy of A. Morritt, O'Brien Institute.)

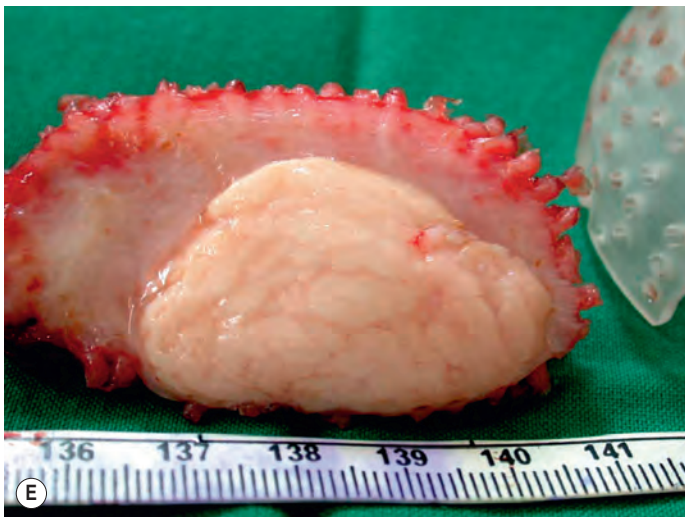
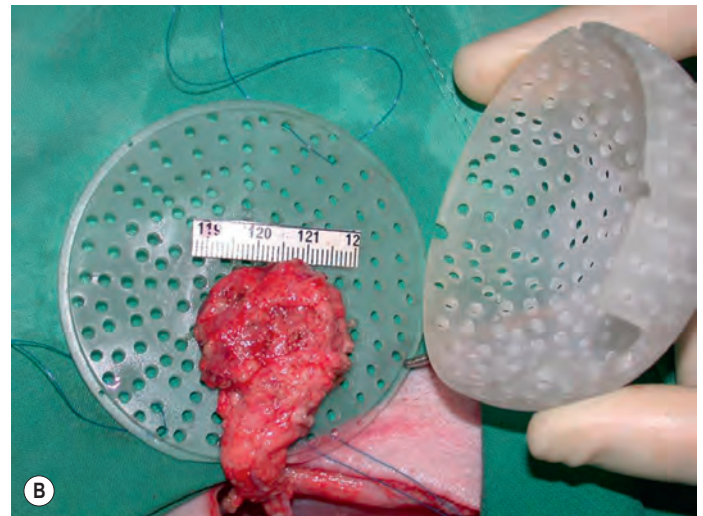


Fig. 16.24 (A) Chambers in pig model, 80 mL volume. (B) 5 mL volume fat flap on epigastric pedicle inserted into the chamber. (C) Buried for 6 weeks. (D) Removal at 6 weeks, filling the chamber. (E) Approximately 50% volume is new adipose tissue.

expansion of the flap from approximately 30 mL to 210 mL (Fig. 16.25A,B). Conversely, the flaps in the remaining three patients failed to expand and instead were encased in a thick fibrous capsule. Although the trial was unsuccessful, the unquestionable finding of stable tissue growth to the chamber's capacity in one of the patients, which was stable at 6

months after chamber removal (Fig. 16.25C), provides a proof-of-concept that clinically relevant volumes of autologous tissue can be generated using the tissue-engineering chamber in humans. The difference in the consistency of results within this trial and in comparison to those obtained in animals warrants further investigation.

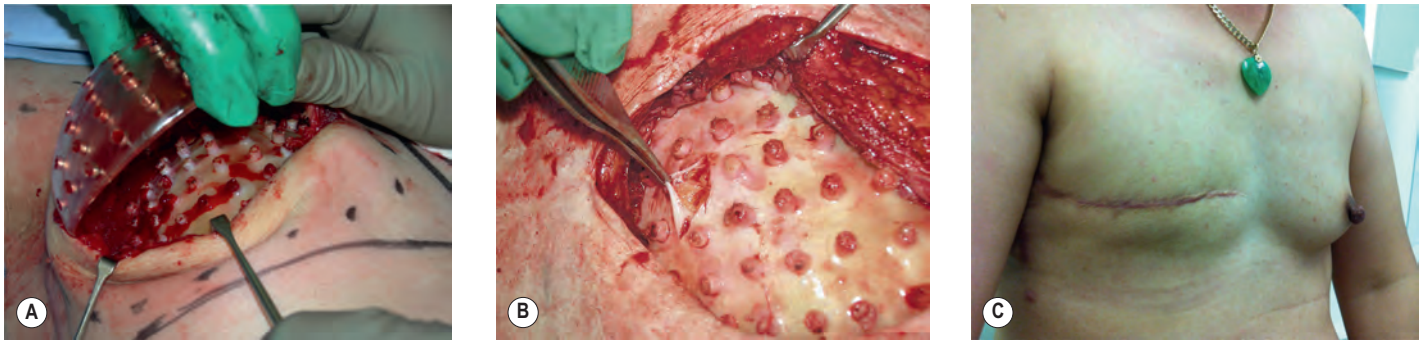


Fig. 16.25 (A) Intraoperative view upon chamber removal. The space is completely filled with fibro-fatty tissue surrounded by a fibrous capsule. Original flap volume was 30 mL and chamber space 210 mL. (B) Detail of tissue generated inside the chamber showing adipose tissue under fibrous capsule. (C) Patient at six months after chamber removal. Newly formed tissue remained stable and softened to a “fat-like” consistency. (From Morrison WA, Marre D, Grinsell D, et al. *Engineering of adipose tissue in humans using the tissue-engineering chamber: a pilot study*. EBioMedicine. 2016; in press.)

Emerging technologies

A range of engineering and technology developments that may significantly impact tissue engineering have emerged over recent years.

3D printing

The most striking development is additive manufacturing via 3D printing, sometimes termed bioprinting or bioplotting

when biological components are included. Whilst this technology has been known for processing plastics for over 30 years, major improvements in the last decade have led to simultaneous reductions in the costs involved and dramatic increases in flexibility. Various types of printing equipment can now be used to produce three-dimensional objects from computer-aided designs (CAD) simply and affordably, as illustrated in Fig. 16.26. At its simplest, a 3D printer resembles a hot-glue gun or syringe delivery system that lays down droplets or fibers of a chosen material in 3D patterns built up

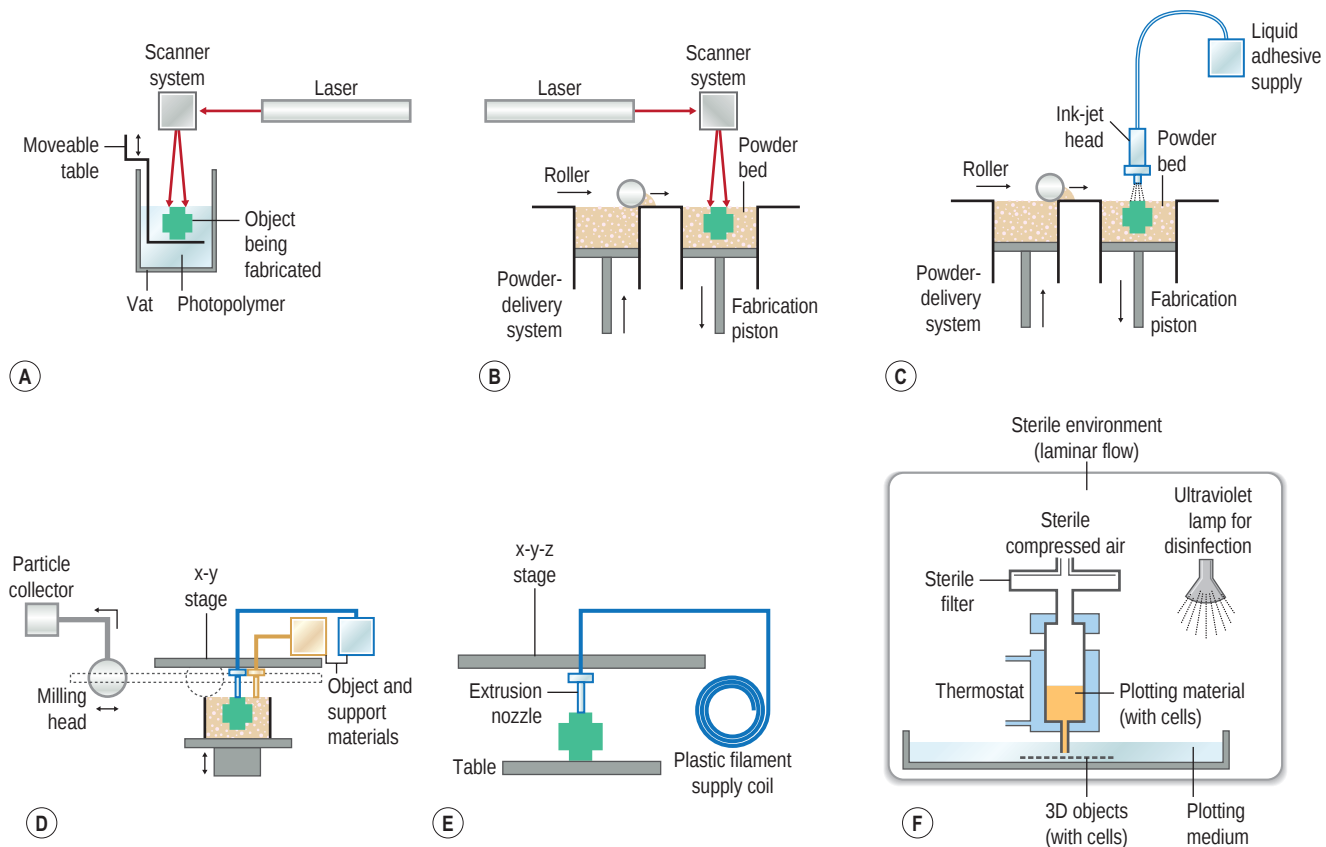


Fig. 16.26 Methods of producing three-dimensional (3D) biomaterial constructs via solid freeform fabrication. (A) Stereolithography. (B) Selective laser sintering. (C) 3D printing. (D) Wax printing. (E) Fused deposition modeling. (F) Bioplotter. (A–E, From *The Worldwide Guide to Rapid Prototyping* website © Copyright Castle Island Co. All rights reserved. F, From Hollister SJ. *Porous scaffold design for tissue engineering*. Nat Mater. 2005;4:518.)

layer by layer as the printer nozzle and/or printing stage move according to the CAD requirements. A wide variety of materials can be processed using different kinds of 3D printers, including polymers, hydrogels, metals, ceramics and even living cells. Many detailed reviews have been published on aspects of this technology and its potential in tissue engineering in recent years.^{88,175}

Many 3D printers and other forms of rapid-prototyping equipment are limited to a certain category of raw materials, e.g., photo-polymerizable or melt-processable polymers with specific physical properties. However, this limitation is also being overcome with printers such as the 3D-Bioplotter (EnvisionTEC GmbH), which are able to print in numerous user-developed materials including melt-processed polymers, hydrogels and viable cells.^{175,176} It is also possible in many devices to print multicomponent mixtures in defined patterns to create more complex objects. Challenges remaining to be resolved with this rapidly evolving technology include the potential of damage to cells and biomolecules during printing due to shear forces in the nozzles, particularly when high spatial resolution is desired. Different printing methods have limitations in material choices and printed construct properties such as pore and fiber size ranges, construct surface properties (e.g., roughness) that can affect cell-material interactions, as well as accuracy, processing cost and speed. Appropriate quality control, predictability of properties such as construct mechanical strength and defect frequencies, the ability to print in a diverse range of medical grade materials, as well as regulatory and industry guidance are areas for further improvement before this technology can be widely adopted in tissue engineering.¹⁷⁷

3D printed polymer scaffolds have been used clinically in a range of applications, mainly for hard tissue repair, typically by creating a customized implant using medical imaging data for a particular tissue defect in a patient. Notable examples include scaffolds for craniofacial bone repair and some recent reports on airway splints for tracheobronchomalacia.^{95,177} Such biodegradable scaffolds or implants are sometimes termed “4D” as they change with time, ideally resorbing as the patient’s tissues develop.

Another area of rapidly increasing activity is production of tissue- or organ-on-a-chip modules often created using microfluidic devices and 3D printing. Such constructs rely on tissue engineering principles and provide opportunities to study tissue development, diseases and screen drugs in more realistic *in vitro* environments.^{178,179}

While biofabrication via 3D printing facilitates the manufacture of custom-designed tissue engineering constructs with excellent spatial control of the initial distribution cells and biomaterials, the major challenge of achieving timely vascularization in 3D tissue engineering constructs discussed above for constructs made in other ways, still applies for 3D-printed constructs. This is often neglected in reports about the potential of this technique, especially in the media where hype sometimes overtakes reality. Research to address this problem has included inclusion of interconnected channels in 3D-printed constructs to allow perfusion *in vitro* and in a recent development, Kolesky *et al.* used a custom-made bioprinter to fabricate heterogeneous constructs that included multiple cell types and vascular channels lined with endothelial cells.¹⁸⁰

In vitro bioreactors

Cell culture in 3D constructs presents challenges in delivery and removal of nutrients and waste products in the absence of a blood supply.¹⁸¹ The delivery of oxygen is challenging due to its relatively low solubility in cell culture media and the time required for diffusion to occur into human-scale 3D constructs. Delivery of macromolecules such as growth factors also presents challenges due to their large size and thus relatively slow diffusion. In addition, mechanical forces, hydrodynamic conditions and electrical stimulation can significantly affect cellular processes and tissue development. Therefore, advanced bioreactors may be helpful to control the microenvironment of cells *in vitro* to encourage the desired cellular processes and tissue development whilst also optimizing the mass transport of oxygen, nutrients and waste products to allow 3D tissue constructs to be developed.¹⁸²

Computational modeling

Mathematical modeling can assist in design of tissue-engineering constructs and processes, providing insights into factors governing tissue growth. For example, different cell-seeding patterns and timing can be investigated using a mathematical model of a tissue-engineering scaffold during vascularization *in vivo* to provide insights into oxygen concentration distributions and cell migration rates. Such models are necessarily simplifications of the complexity of the biological processes at play but may aid experimental design and interpretation and so help reduce trial-and-error experimentation and animal use.^{183,184}

Testing and characterization of tissue engineering approaches

Characterization of new or modified biomaterials, cells, and methods for tissue engineering is critical to their potential pathway to clinical trials and ultimately to clinical and commercial success. Systematic testing is not only a requirement of regulatory and ethical approval during the development process, but also crucial to developing understanding and thus being able to improve tissue-engineering methods further. Testing should aim to allow prediction of the long-term safety and efficacy of the tissue-engineering approach under consideration. Ideally, *in vitro* testing would be used to screen tissue-engineering constructs and methods in order to minimize animal testing for ethical reasons. However, it remains a significant challenge to predict *in vivo* responses from *in vitro* tests and so significant animal testing is normally required before clinical trials.

Standardized testing methods are highly desirable so that objective comparisons can be made between different approaches and construct components across different laboratories. Testing should be undertaken under conditions simulating the targeted tissue-engineering application, rather than relying on test results for the same material in different applications where phenomena may differ significantly.¹⁸⁵ Physicochemical characterization of biomaterials and constructs made from biomaterials should be undertaken to ensure the targeted composition, absence of significant residues or impurities, and desired morphology are achieved.

Materials which are nominally the same may perform differently in tissue-engineering applications due to differences such as the presence of impurities, differences in molecular weight or polydispersity in polymers, or variations in surface properties.

Risks, ethics and regulation

Risk management is a critical consideration in clinical and commercial tissue-engineering efforts. A number of potential products developed early this century suffered from problems with regulatory trials and product launches, along with challenging investment conditions internationally.¹⁸⁶ Tissue-engineering approaches have significant potential benefits to patients and the health system but also involve risks, which may include human error (e.g., mix-ups of autologous cells), biomaterial performance variations from predictions (e.g., changes in degradation rates *in vivo*), quality control problems (e.g., microbiological contamination), and variations in patient-specific responses. Most of these can be minimized by rigorous management and scientific processes (e.g. through GMP process requirements, process automation and quality control), whilst patient-specific responses will only be fully assessed once sufficient clinical trial data have been collected. Many of the commercial successes in the field of tissue engineering to date have avoided the risks involved in delivering biological materials, rather using acellular products.¹⁸⁶

The ethical considerations related to tissue engineering have been reviewed^{187,188} and many of these are common with other fields of medicine and biomaterials. The sources of biological material to be used, particularly the potential use of ES cells, are, unsurprisingly, prime considerations. The extent of animal testing is a further issue of concern, which may be partly addressed by effective *in vitro* testing and well-designed experimental approaches, as discussed above. Animal trials should be designed to simulate the final clinical application as closely as possible to avoid incremental approaches to the final design with numerous animal trials at every stage.

The regulatory approvals required for tissue-engineered products depend on the jurisdiction involved and have evolved significantly over the last decade around the world. In the case of the US Food and Drug Administration (FDA), products may be characterized as tissues, biological products, medical devices, or combination products and numerous standards and guides have been developed for particular categories of products.^{189,190} The ISO10993 series of standards addresses "Biological Evaluation of Medical Devices" and numerous ASTM guides provide details on testing and characterization requirements for different types of tissue engineering products.

Case studies and status of tissue engineering for specific tissues

Skin tissue engineering

Biological wound dressings have been long-established from cultured sheets of keratinocytes,¹⁹¹ and together with skin banks this has saved the lives of many burns patients.

However, graft durability and functionality is often poor, with wound contraction, scar formation, and impaired sensation being frequent complications in addition to graft failure. To improve this, skin tissue engineering has focused on generating a dermal component in addition to the epidermal layer. Such tissue-engineered skin substitutes would function beyond simple wound coverage and barrier protection. They could be applied in the treatment of chronic wounds with impaired wound healing such as diabetic ulcers, in skin disease models for example with vitiligo and psoriasis, and for drug and cosmetic testing. Additionally, oral mucosa tissue engineering draws many similarities with skin,¹⁹² and this will no doubt be useful in craniofacial reconstructions.

The principles of skin tissue engineering follow the same concept as other tissues and involve cells, scaffold, and vascularization. Cell sources include fibroblasts to promote collagen and other ECM structural integrity but also to address the fundamental problem of biofilm that protects bacteria from attack by neutrophils and renders local fibroblasts senescent. Live fibroblasts can be incorporated into the implant to attract and activate neutrophils through the secretion of proinflammatory cytokines and growth factors.^{193,194} Other cell types include epidermal-derived stem cells,¹⁹⁵ and MSCs especially for wound healing,¹⁹⁶ and melanocytes.¹⁹⁷ Bulge cells from hair follicles and co-cultures, especially with neonatal dermal fibroblasts, offer some hope of regeneration of functional skin elements, including hair follicle and sebaceous glands.¹⁹⁸ Cutaneous nerve regeneration may be enhanced through the addition of Schwann cells, or epidermal-derived stem cells and other MSCs which are capable of differentiation into both neurons and Schwann cells.¹⁹⁹

Scaffolds are a key aspect of engineered skin. Substitutes initially served as passive matrices for ingrowth from the wound bed full of blood vessels and dermal elements, but more recently complex structures have been developed comprising of biomimetic proteins and material, 3D culture techniques, and altered surface chemistry and topography to influence cell adhesion, growth and differentiation, durotaxis, spatial cueing, and mechanoregulation.^{200,201} They can also facilitate nerve regeneration,¹⁹⁹ and may include antibacterial agents such as PLGA films and polylactic acid nanofibers loaded with silver ions or nanoparticles.^{202–204}

Current products suffer from poor integration to the wound bed as a result of inadequate vascularization and this impacts on the survival of implanted cells. Recent efforts to address this include the use of angiogenic biomaterials and prevascularization of constructs (covered in earlier sections), as well as the use of stem cells such as adipose-derived stem cells which abundantly secrete angiogenic growth factors and can also contribute directly to regeneration by differentiating into fibroblasts, epithelial, and endothelial cells.²⁰⁵

Adipose tissue engineering

Adipose tissue engineering holds great interests to plastic surgeons for reconstruction of soft tissue deformities such as Poland syndrome, Romberg syndromes, aging, breast post-mastectomy and traumatic deformities, burns, and postirradiation defects.

Adipocytes are fragile, prone to ischemic death,²⁰⁶ very difficult to grow in cell culture, and do not proliferate *in vivo*. Consequently, precursor populations derived from bone

marrow or fat SVF and sorted by adherent cell culture or fluorescence-activated cell sorting (FACS) are the preferred cell source for the traditional loaded-scaffold paradigm of tissue engineering. However, this direction has been singularly unsuccessful for fat, no matter what scaffold is chosen, and most clinically focused research is returning to modifications of fat injection, possibly with matrix material as a more likely route to clinic.

Attempts to understand the fate of fat-grafting dates back almost a century when Marchand²⁰⁷ grafted fat onto the brain of animals. Upon exploration, he identified two cell types: (1) fat, which he interpreted as having survived a graft; and (2) histiocytes, which had come from the hosts and appeared to be turning into fat, which he labeled as replacement. Since then, a long debate ensued as to whether cells in grafted fat survive or signal endogenous fat production. When we inserted human fat grafts into our mouse chamber tissue-engineering model containing Matrigel® and FGF-2, new fat formed but it was of mouse origin (Fig. 16.27). Similarly, when

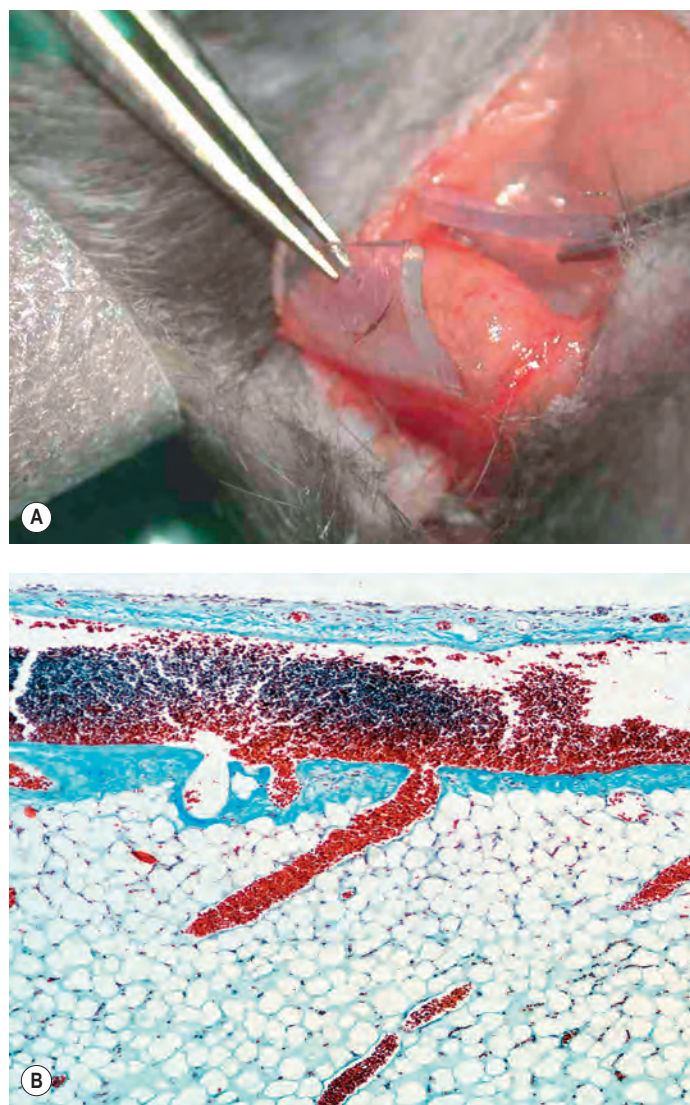


Fig. 16.27 (A) Spontaneous endogenous fat formation in Matrigel® in a mouse model of tissue engineering after insertion of a small nonvascularized fat allograft. (B) Normal fat tissue grown in the chamber. Note the extensive vascularization sprouting from the vascular pedicle. (Courtesy of F. Stillaert, O'Brien Institute.)

FACS-sorted or SVF-derived human ASCs or bone marrow stem cells were implanted, endogenous fat formed.²⁰⁸ If the fat graft or stem cells are substituted by an inflammagen such as yeast particle zymosan, fat also forms in Matrigel®.²⁰⁹ Taken together with the early appearance of macrophages in the chamber and their critical role in angiogenesis and adipogenesis as shown by macrophage ablation studies,²¹⁰ it suggests that the signaling mechanism by which fat grafts stimulate fat growth is an inflammatory one. This is consistent with the emerging notion that MSCs largely function through their paracrine effects especially to promote angiogenesis and cell signaling. The cytokine profile of the mouse chamber contents clearly shows inflammatory angiogenesis predominating for the first 7 days, at which time it changes to adipogenesis with the appearance of peroxisome proliferation-activated receptor- γ and other markers.²¹¹ Whether this event sequence is peculiar to Matrigel® matrix is not yet clear. Nevertheless, increasing evidence suggests that initial cell death within fat grafts is followed by neoadipogenesis, which is mediated by stem or progenitor cells within the grafted material with the recruitment of host cells at the implantation site.^{212,213} This is supported by recent clinical studies reporting the enhanced survival of fat grafts enriched with SVF/ASCs when compared to fat grafts alone.^{214,215} However, whether the fat graft itself survives at least in part remains unanswered, with a wide variability of results in the literature.²¹⁶ Furthermore, questions remain as to whether the stem cells themselves survive and contribute directly to new fat, or if they represent a concentrated dose of inflammatory paracrine factors which induce endogenous fat production.

Matrix plays a key role in adipogenesis, as does angiogenesis. Multiple synthetic and natural scaffolds have been trialed *in vitro* and *in vivo* with and without FGF and/or seeded cells. Matrigel® is both angiogenic and adipogenic,²¹⁷ and several Matrigel® substitutes are under study, including derivatives of muscle (myogel)⁵⁵ and adipose-derived matrix (ADM).²¹⁸ The ultimate clinical product would be an adipogenic injectable matrix gel with or without processed lipoaspirates. ADM has so far shown promise in stimulating the adipogenic differentiation of ASCs both *in vitro* and *in vivo*,²¹⁸ and can be used as an off-the-shelf product to regenerate subcutaneous fat in soft tissue defects created in the rat back.²¹⁹

Another important area is the role of mechanical forces that influence cell behavior, including differentiation. We believe this is critical to the growth seen in the chamber space, particularly in those models where there was no matrix or seeded cells such as the adipose tissue growth seen in the pig model (see Fig. 16.24) and clinical study (see Fig. 16.25), corroborated more recently by others using a rabbit model.²²⁰

Muscle tissue engineering

Tissue engineering of skeletal muscle has potential *in vivo* applications for the treatment of muscular dystrophy, muscle loss from injury and post-tumor resection, chronic denervation, and targeted delivery of proteins and drugs by gene transfection of muscle cells. *Ex vivo* applications could include models for the study of exercise physiology or muscle diseases or drug screening. It could also in theory find a commercial use for tissue-engineered meat production from animal stem cell sources.²²¹

Muscle is unique functionally with its densely packed parallel-aligned multinucleated muscle fibers which contract axially through calcium-sensitive actin and myosin filaments. This in turn involves neural connections functionally linked through acetylcholine release and its receptors. Addressing this specialized architecture with the incorporation of vascular and somato-sensory elements to create fully innervated, vascularized skeletal tissue that can be transplanted and function *in vivo* remains a major challenge.

Cells used for muscle tissue engineering include myoblasts, the progenitor cell to mature myocytes which can be isolated from skeletal muscle and expanded *in vitro*. However, differentiation in 2D culture after extended passaging is difficult, and requires ECM coating or 3D culture to facilitate myoblast alignment and differentiation.^{222,223} Another cell source includes the more immature satellite cells, which are resident stem cells in skeletal muscle residing below the basal lamina of myofibers. They represent 2–7% of the cell population in adult muscle and are capable of self-assembly into new myotubes following injury and stimulation.²²⁴ However, expansion of these cells after isolation is problematic, with reduced proliferation and regenerative capacity with prolonged culture.²²⁵ Satellite cells can be replenished by pericytes, which are found in the walls of small blood vessels.²²⁶ Pericytes isolated from a wide variety of tissue including skeletal muscle are also capable of myogenesis both *in vitro* and *in vivo*, regardless of tissue origin.²²⁷ They are closely related to mesoangioblasts, which are perivascular cells found in larger vessels and are also capable of contributing to muscle regeneration.²²⁸ Both pericytes and mesoangioblasts are phenotypically similar to MSCs, which are also attractive candidates. MSCs can be derived from a wide variety of tissues, as discussed above, home into sites of injury, secrete useful paracrine factors, and directly contribute to new muscle.²²⁸ More recently studies have also focused on the generation of myoblasts, myogenic MSCs, and mesoangioblasts from pluripotent stem cells such as iPS or ES cells.^{229–232} This opens a gateway for the use of autologous cells for tissue engineering, as well as the transplantation of genetically corrected cells for conditions such as muscular dystrophy.²²⁹

Strategies to improve the myogenic differentiation of cells include the use of 3D perfusion bioreactor systems²³³ and co-culture of myoblasts with various other cells such as SVF (containing ASCs)²³³ and fibroblasts.²³⁴ Co-culture with neural tissue in a 3D matrix can also enhance *in vitro* muscle function,²³⁵ as well as generate neuromuscular junctions with functioning acetylcholine receptors.²³⁶ Electrical stimulation of myoblasts in 3D collagen culture mimics nerve stimulation and promotes differentiation to myotubes and ECM deposition.²³⁷ Mechanical stretch or force organizes myoblasts into functionally aligned myotubes and favorably influences fiber diameter and cell number^{238,239} by myofilament gene regulation and protein expression.^{240,241} *In vitro* preconditioning of myoblasts by cyclic strain in a bioreactor improved the contractility of engineered tissue.²⁴² Other specialized culture systems include the co-culture of myoblasts with fibroblasts on Seran wrap or laminin-coated plates stretched out between pins. This led myoblasts to orientate themselves axially and separate from the wrap upon differentiation to assemble into a cylindrical core of contractile muscle using the pins as tendon-like anchors, which were termed as myoids.^{243–245} More recently, sophisticated approaches to cell alignment

include the manipulation of the cell culture surface topography using nano/micro-patterning techniques, ECM printing, as well as the application of mechanical strain and electromagnetic fields in order to generate myotubes and skeletal muscle sheets.²⁴⁶

ECM compositions play a key role in the alignment and differentiation of myoblasts. Hydrogels facilitate self-assembly of suspended cells into transplantable constructs, and collagen,²⁴⁷ fibrin,²⁴⁸ alginate,²⁴⁹ hyaluronic acid,²⁵⁰ PEG,²⁵¹ and extracellular matrix derivatives such as Matrigel^{®252} and myogel²⁵³ have been used. Various synthetic matrices, including PLGA mesh,²⁵⁴ PCL,²⁵⁵ chitosan,⁹³ glass fibers,²⁵⁶ electrospun nanofibers,^{257,258} and wavy silicone surfaces²⁵⁹ influence regulation of cell alignment differentiation and proliferation but the elasticity, toxicity, and biodegradability are critical to *in vivo* application. Decellularized biological scaffolds may be more physiologically attuned with this regard, as they contain relevant ECM components in their relative compositions, are non-immunogenic, have a preformed shape, and likely retain biologically active cytokines and growth factors and functional cues. Decellularized scaffolds from porcine urinary bladder (MatriStem[™]) have been used to stimulate local muscle regeneration in patients with volumetric muscle loss following severe leg injury.²⁶⁰ By placing these scaffolds within the injured muscle close to viable tissue followed by intensive physical therapy, biopsy at 6–8 months showed new muscle tissue with resorption of the scaffold, correlated with CT/MRI imaging. Improved functional outcomes were reported in 3 out of 5 patients despite an original muscle loss ranging from 58–90%. It is expected this could be further optimized through the addition of cells to the scaffold, such as in a study where decellularized skeletal muscle was reseeded with myoblasts, fibroblasts, perivascular stem cells, and endothelial cells and used to reconstruct a rat abdominal wall defect.²⁶¹ This approach has also been taken to reconstruct a bioartificial limb from decellularized rat and primate forearms.²⁶² Scaffolding from the soft tissue including muscle was recellularized in a bioreactor with endothelial cells, myoblasts, and fibroblasts followed by electrical stimulation and coverage of the forearm with a skin graft (Fig. 16.28). Despite no integration of neural tissue, the rat paw was seen to clench and unclench in response to electrical stimuli with approximately 80% the strength of a newborn rat. Functional anastomosis of blood vessels could be achieved upon transplantation of these forearms with preserved response to electrical stimuli. Although this remarkable proof-of-concept study still requires many steps to become clinically relevant, it provides encouragement in the field of decellularized scaffolds.

Vascularization remains a large hurdle in the upscaling of engineered tissue *in vitro*, and the survival of transplanted tissue. In recognition of this, *in vitro* approaches may combine myogenic cells with endothelial cells within 3D scaffolds,^{263,264} or combine the delivery of growth factors such as VEGF or insulin-like growth factor 1 together with cells in a scaffold.^{247,265} Scaffolds themselves can be tailored to have sustained release of these growth factors to mitigate their short half-life, and encourage blood vessel ingrowth from the host into the engineered tissue upon transplantation.²⁶⁶ Applying intrinsic vascularization is another option, and we have used both the mouse flow-through pedicle model and rat arteriovenous loop model to demonstrate the survival of implanted myoblasts.^{252,267} Cell survival can be enhanced through the use



Fig. 16.28 Recellularization of decellularized rat arm scaffolds. **(A)** Progressive decellularization of whole rat arms. **(B)** Recellularization of arm scaffold. (A, Reprinted from Jank BJ, Xiong L, Moser PT, et al. *Engineered composite tissue as a bioartificial limb graft*. *Biomaterials*. 2015;61:246–56, with permission from Elsevier. B, Reproduced with permission from Dr. Harald C. Ott and Dr. Bernhard J. Jank, Massachusetts General Hospital and Harvard Medical School.)

of techniques such as *in vitro* preconditioning to stimulate pro-survival signaling pathways (Akt and ERK1/2), or *in vivo* prevascularization with delayed seeding to prepare a dense capillary bed prior to cell delivery. However, to generate larger volumes of vascularized three-dimensional skeletal muscle it is likely that a combination of vascularization strategies would be required during both the *in vitro* and *in vivo* phase, with amalgamation of advances in cell co-culture, growth factor delivery, scaffold tailoring and intrinsic vascularization. This will need to be accompanied by appropriate electrical stimulation and neuronal integration to maintain the growing muscle tissue.

Tissue engineering of nerves

Nerves in different locations have distinct microenvironments and thus the optimal tissue-engineering strategies for each will differ. Tissue-engineering strategies may be used for guided nerve regeneration using, for example, degradable biomaterial tubes or scaffolds. There are now a range of FDA/Conformit Europe approved neural scaffolds available which largely consist of collagen I, but include PVA, PCL and decellularized matrix derivatives.²⁶⁸ Hollow tubes can function effectively as nerve guides for gaps of up to 10 mm in the peripheral nervous system under a range of clinical situations. For example, tubular collagen nerve guides (NeuraGen®, Integra LifeSciences) are being used clinically to treat peripheral nerve injuries.²⁶⁹ The critical gap length that may be successfully treated using nerve guides can be longer than 10 mm in primates and can be further increased by addition of cells and cell supports such as biomaterial fibers or hydrogels.²⁷⁰ It has been shown that use of oriented hydrogel matrices (e.g., fibrin or collagen) within nerve guides results in a larger critical gap length than use of the same matrices without alignment. Electrospun fibers can provide mechanical support to guide nerve regeneration, depending on their diameter, alignment, and spacing, and nanofibers may also be developed within a hydrogel.²⁷¹ Including conductive materials such as gold nanoparticles or carbon nanotubes can facilitate the use of electrical stimulation, which can increase neurite outgrowth and maturation.^{272,273} Schwann cell grafts including those generated from iPSCs,^{274,275} and the addition of controlled-release vehicles containing drugs or neurotrophic

factors can also increase the success of tissue-engineering strategies for nerves.^{268,276} Three-dimensional printing could be used in the fabrication of these nerve guidance conduits, and there is potential to integrate this technology with bionic limbs by connecting bioengineered scaffolds as nerve guides to electrodes in the prosthetic limb.

The environment and cellular responses to injury in the central nervous system tend to inhibit regeneration. Stem cell therapies for spinal cord injury including several human trials have shown some regenerative responses, but the mechanisms of how they may repair the spinal cord are not well understood.²⁷⁷ Direct contribution to new tissue, release of trophic factors, and modulation of inflammatory cytokines particularly in the early stages of injury have been postulated. Tissue engineering could be applied in this area to enhance the delivery of regenerative cells, scaffolds, and neurotrophic factors to promote axonal regrowth following injury. Scaffolds or hydrogels can aid cell adhesion, retention and differentiation, or be used to deliver growth factors and drug molecules, and oriented pores and channels can guide axonal growth.²⁷⁸ Interestingly, the use of an acellular scaffold may forestall immediate scarring of the spinal cord following injury, providing a more permissive regenerative environment.²⁷⁹

Tissue engineering of blood vessels

A number of strategies to tissue engineer blood vessels *in vitro* or *in vivo* as an alternative to autografts, allografts, or nondegradable polymer prostheses have been developed and tested in animal models and in the clinic with promising results.²⁸⁰ The engineering of capillary networks in scaffolds has been covered earlier in the chapter, but advances have also been made in the development of larger macrovessels. Collagen-based scaffolds containing a polyester mesh are available commercially (Omniflow II from Bio Nova International) and are used clinically as a biosynthetic vascular graft for hemodialysis access.²⁸¹ Decellularized veins have been used as allografts, although a high rate of aneurysmal and thrombotic complications have been noted.²⁸² Grafts have also been made by culturing allogeneic smooth muscle cells on PGA scaffolds to encourage ECM deposition and remodeling of the synthetic material, followed by detergent-based removal of these cells to retain only the ECM skeleton.²⁸³ This Humacyte technology is

now undergoing clinical trials. More complex scaffold-based vascular grafts have also been developed, relying on micro-printing and electrospun nanofibers from natural and synthetic polymers to fabricate a tri-layered structure mimicking the layers in large vessels, with increased mechanical strength.²⁸⁴ These approaches rely on the rapid revascularization of the scaffold by host cells after implantation to form a new blood vessel. Loading scaffolds with cells prior to implantation has also been attempted,^{285,286} and can use various cells other than endothelial cells including endothelial precursor cells, ASCs, pericytes, and MSCs.²⁸⁷ Cells can also be incorporated as micro-tissue units into scaffolds in the form of spheroids.²⁸⁸ However, the use of cells in macrovessel tissue engineering has focused more on a scaffold-free approach. This relies on cell sheet engineering, where sheets of cultured dermal fibroblasts and their surrounding ECM are rolled into tubes which are then seeded with the patient's endothelial cells.²⁸⁹ This technology has since progressed to clinical trials as the Lifeline tissue-engineered blood vessel.^{289–291} In another alternate strategy, Campbell *et al.* have developed an intraperitoneal graft model where silastic tubing is implanted into the peritoneal cavity *in vivo*, leading to a foreign body reaction consisting of an inner collagen layer, middle myofibroblast layer and outer mesothelium which form tubular “vessels” comprised of autologous cells. These vessels have been successfully grafted into the circulatory system of the host animal where they were shown to remodel in response to the new environment and remain patent for up to 16 months in rabbits.^{292,293}

Bone tissue engineering

Significant research efforts have been made to tissue engineer both load-bearing and non load-bearing bone to meet the demands for alternatives to autografts or allografts, which have their inherent disadvantages and supply limitations. However, limited translation to clinical application has occurred to date.^{294,295} Bone tissue-engineering strategies generally involve a biomaterial scaffold of suitable mechanical strength with or without added cells and/or biomolecules to encourage bone growth. Vascularization has often been neglected in bone tissue engineering, but is increasingly recognized to play a role beyond simple cell survival and nutrient/waste exchange, as normal bone repair occurs in close association with blood vessels and angiogenic factors, particularly VEGF, play a role in initiating and promoting osteogenesis.²⁹⁶

Tissue-engineered constructs for bone should be osteoconductive to allow bone cells to adhere, proliferate, and migrate. A range of ceramics (e.g., β -tricalcium phosphate and hydroxyapatite) and polymers have been reported to meet this requirement and a number have been used as bone substitutes clinically. Slowly degrading polymers, such as PLA and PCL, have been widely investigated to produce tough porous scaffolds for bone tissue engineering. FDA-approved PCL-based scaffolds have been developed for bone tissue engineering (Osteopore International), and used clinically as burr plugs and sheets for orbital floor reconstruction in more than 1000 patients.^{95,297} Altering the surface topography of some of these more traditional bone substitutes, such as the coating of ceramic titanium dioxide scaffolds with nanoparticles made of the same material, may further augment their regenerative potential.²⁹⁸

Scaffolds which are osteoinductive have also been produced and shown to enhance bone growth. A wide range of natural biopolymers have been studied for bone tissue engineering, including collagen, gelatin, silk fibroin, chitosan, alginate, and hyaluronic acid.²⁹⁹ Among inorganic compounds, bioactive glasses composed of silica-containing calcium, sodium and phosphorous oxides have been termed “bioactive” because they can form strong bonds to hard and soft tissues *in vivo*.³⁰⁰ These materials have been marketed commercially as Bioglass and used clinically, primarily in nonload-bearing applications.

Composite materials are attractive as they can be used to control biodegradation and can overcome brittleness. This strategy mimics the composite structure of bone, being an inorganic–organic composite structure. Examples include nanocomposite structures combining collagen and calcium phosphate, as well as chitosan–gelatin and ceramic scaffolds.^{299,301} Suspensions or pastes of ceramic or composite materials may also be used in surgical repair or via injection to encourage bone growth for small-volume repairs.

In addition to the influence of the scaffold, the osteoinductive growth factors, bone morphogenic proteins (BMPs), may be used to enhance bone tissue growth. Other growth factors (e.g., TGF- β_1 , FGF-2, platelet-derived growth factor) may also enhance bone formation, as summarized by van Gaalen *et al.*³⁰⁰ Tissue engineering utilizing BMPs has progressed to a number of clinical trials, primarily in spinal surgery, showing some promising results.^{92,300} VEGF plays a dual role in angiogenesis and osteogenesis, and its encapsulation in PLGA scaffolds has been shown to increase both vascularization and bone formation.³⁰² However, the direct use of growth factors in a clinical setting will need to proceed with caution with particular attention to safety and optimizing delivery systems. Using cells that secrete osteoinductive and angiogenic growth factors may be another option. This includes cells such as MSCs, as well as endothelial cells, including endothelial progenitor cells, which have been shown to secrete BMPs and TGF- β s and contribute to bone healing.^{303,304} Furthermore, the addition of osteogenic cells, such as osteoprogenitor cells found in the bone marrow or periosteum, MSCs, and more recently iPSC-derived MSCs or osteogenic progenitors, particularly in addition to supportive cells and growth factors, may accelerate bone repair through direct tissue contribution but also ECM deposition and interaction with the host environment.^{295,296}

Cartilage tissue engineering

Tissue engineering of cartilage is relatively well developed as the problem is simplified by not requiring vascularization within the developing tissue. Several cell and tissue-engineering treatments for cartilage repair have been established clinically. However, clinical use is not widespread as yet due to limitations in efficacy, consistency, and applicability.³⁰⁵ Autologous chondrocyte implantation for articular cartilage repair has been approved by the FDA and implemented clinically (Carticel®, Genzyme Biosurgery, US).²⁹⁴ Although this procedure has shown good clinical outcomes, it is labor-intensive in the cell expansion and multi-stage procedure, and limited in the defect size that can be treated.^{306,307}

Biomaterial support structures may be used to treat larger cartilage defects, deliver cells, and provide critical mechanical support until the tissue is sufficiently developed. A possible timeline for cartilage repair using a biomaterial implant is

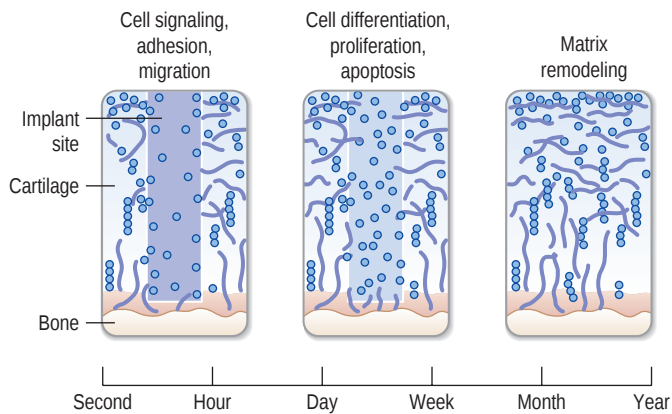


Fig. 16.29 A timeline for cartilage tissue engineering from *in vivo* implantation to formation of the final tissue. (From Palsson BO, Bhatia SN. Tissue Engineering. Upper Saddle River, NJ: Pearson Education, 2004.)

shown in the idealized schematic in Fig. 16.29. The 3D arrangement of chondrocytes is important to their function and the ECM synthesis required for tissue development, and this may be encouraged by suitable biomaterial scaffold design.^{69,308} Native articular cartilage is not isotropic but contains zones of different ECM and cell organization and function. Current research aims to develop biomaterial scaffolds which mimic this feature of cartilage more effectively to achieve engineered tissues with the normal zonal organization.^{305,309}

A range of biodegradable polymers, including PLGA, PCL, hyaluronan, gelatin, and collagen, have been used to produce scaffolds and microspheres to support chondrogenesis.^{82,306,308,310} Matrix-induced autologous chondrocyte implantation is similar in procedure to routine autologous chondrocyte implantation, but it relies on scaffold technology where cells are expanded and cultured on porcine collagen type I/III membranes prior to implantation.³¹¹ Hyalograft (a form of the biomaterial product Hyaff-11 from FIDIA Advanced Biopolymers, Italy) is a hyaluronic acid-based 3D scaffold product for cartilage tissue engineering that has also been used clinically.^{49,306}

The main cartilage tissue engineering approaches are the delivery of cells in a hydrogel or scaffold, the implantation of acellular scaffolds tailored to stimulate chondrogenesis, or scaffold-free techniques involving the culture and implantation of chondrogenic spheroids which may be derived from stem cells such as iPSCs.³¹² The physical microenvironment of the cells is important to tissue development, and can be manipulated during *in vitro* culture using forces such as gravity and hydrodynamic forces from the fluid motion to affect the quality and size of cartilage tissue formed (Fig. 16.30).^{308,313} A number of bioreactor designs have been devised to provide favorable *in vitro* growth conditions for chondrocytes.^{305,310} Other novel aspects being explored include 3D printing, including the use of BioPen technology where cells in an ECM carrier ink could be delivered through a pen nozzle, allowing the filling of small surgical defects as well as precise coverage over bone and cartilage surfaces.³¹⁴

Tissue engineering of other organs

Striking advances are being made in identifying, characterizing, and culturing various stem cells, in tailoring scaffolds

to maximize tissue assembly, and greater emphasis is now placed on the critical role of vascularization in supporting engineered tissue. With this integrated approach, there has been an exponential growth in tissue engineering studies in recent years, with a number of high profile clinical reports.^{315,316}

Using our models of intrinsic vascularization, we have been successful in generating a range of tissues including cardiac tissue from rat neonatal cardiomyocytes,¹⁶² human ASCs,³¹⁷ and human iPSCs.³¹⁸ The chamber has also been used for the implantation of pancreatic islets,³¹⁹ and liver progenitor cells.¹⁶⁵ We have also engineered tissue capable of secreting growth hormone after implantation of mouse pituitary stem

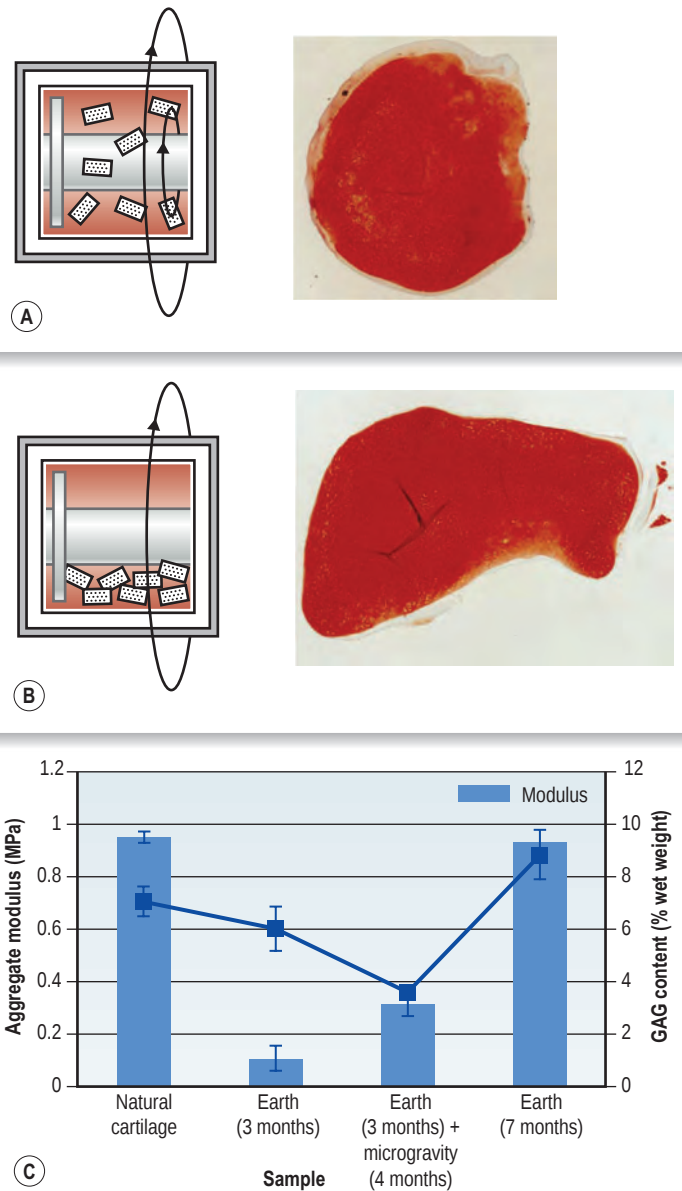


Fig. 16.30 Effects of physical forces on tissue engineering: cartilage grown *in vitro* in microgravity and in Earth's gravity. (A) Tissue constructs obtained from growth in rotating bioreactors on Earth for 3 months and in microgravity for 4 months. (B) On Earth only for 7 months (tissues are stained with safranin-O to show glycosaminoglycan in red). (C) Graph of tissue construct aggregate moduli and glycosaminoglycan (GAG) content. (Based on data from Freed LE, Langer R, Martin I, et al. Tissue engineering of cartilage in space. Proc Natl Acad Sci USA. 1997;94:13885–13890. © 1997 National Academy of Sciences USA.)

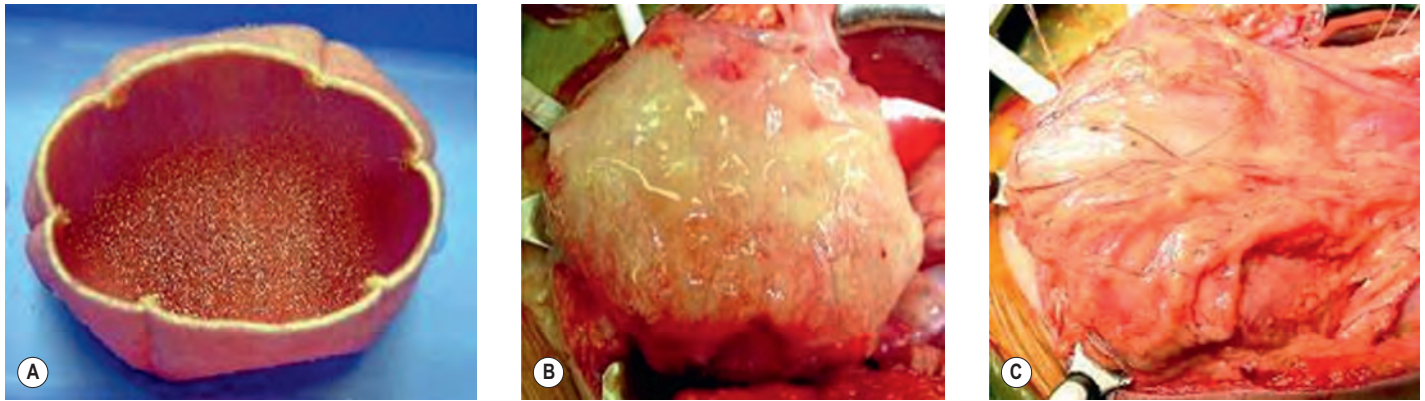


Fig. 16.31 Tissue engineering of the bladder. (A) A biodegradable scaffold was seeded with autologous cells. (B) Anastomosed to the patient's native bladder. (C) Covered with fibrin glue and omentum. (From Atala A, Bauer SB, Soker S, et al. *Tissue-engineered autologous bladders for patients needing cystoplasty*. *Lancet*. 2006;367:1241–1246. © Elsevier 2006.)

cells into a vascularized chamber in mice³²⁰ and restored thymus function in athymic rats after implantation of human thymic tissue in vascularized chambers as evidenced by the postoperative appearance of processed T cells in the blood and by the rejection of skin allografts.³²¹

Most recently, the field has placed particular interest in the use of extracellular matrix scaffolds derived from decellularized tissues and whole organs of various types, including human heart,³²² lungs,³²³ liver,³²⁴ and kidneys.³²⁵ Many pre-clinical studies have demonstrated the recellularization of these scaffolds with various cells including organ-specific cells and other stem cells, with cell attachment and organization into their native compartments to recapitulate tissue architecture. Many of these bioengineered tissues and organs have been implanted in small animal models, and several of these areas have been translated into clinical studies.

An early human clinical trial on organ tissue engineering was led by Atala *et al.* and focused on the bladder. A significant milestone was the report in 2006 that engineered bladder tissue showed promising outcomes in a clinical trial for cystoplasty reconstruction.^{326,327} Autologous cells from a bladder biopsy were seeded on to biodegradable scaffolds and grown *in vitro* prior to transplantation (Fig. 16.31). Bladder function was shown to improve and this was sustained up to 5 years. Atala provided an anecdotal note in 2014 that these patients continued to do well up to 11 years later.³²⁸ However, a recent Phase II trial by a separate group using the same protocol reported no improvement in bladder compliance or capacity, and serious adverse events such as bowel obstruction and/or bladder rupture in 4 out of 10 patients.³²⁹ Atala considers the disparity possibly to be due to a number of reasons. These include variability in patient cells, batch-to-batch manufacturing variability due to an individualized process, genetic variability, and lastly difference in the clinical spectrum of spina bifida patients in terms of their level of spinal cord pathology, bladder innervation, and functional disturbance.³²⁸ While efforts are being made to address these unique issues in regenerative medicine, it is worth remaining prudent and cautiously optimistic while we await the results of the next bladder trials before making any firm conclusions.

In 2008 Macchiarini *et al* reported the transplantation of the first bioengineered trachea in a human patient, based on

reseeding a decellularized tracheal graft with the patient's own epithelial cells and MSC-derived chondrocytes.³³⁰ A 5-year follow-up report noted that the graft remained patent, vascularized, and completely recellularized with normal function and no signs of rejection, although stenosis of the native trachea near the anastomosis required repeated endoluminal stenting.³³¹ This group has also developed a synthetic tracheal graft fabricated from nanocomposite polymer, which was reseeded with a patient's cells in a bioreactor prior to transplantation.³³² Transplantation of bioengineered trachea based on decellularized matrix has also been performed in a paediatric patient.³³³ However, these remain individual case studies and very much like with bladder tissue engineering, expanded clinical studies with long-term follow-up is required before these feats become an accepted treatment.

In 2014, a small pilot study of 4 patients with vaginal aplasia involved the transplantation of vaginal organs created from autologous epithelial and muscle cells obtained from a vulval biopsy and seeded in segments of Surgisis (decellularized porcine intestinal submucosa matrix).³³⁴ This technology could be useful not only for vaginal reconstructions but also for other soft tissue defects, although the lack of integrated vascularization will likely limit the use to thin grafts implanted into relatively well-vascularized sites.

Whilst clinical studies are still few and far between and fraught with technical challenges, we are gradually moving from thin flat tissues (skin, cornea) to tubular (trachea, blood vessels) and hollow viscus organs (bladder), and in the foreseeable future will likely progress to solid organs such as the kidney, heart or liver. Organ regeneration is the grail of tissue engineering, and with the advent of iPS cells this field offers a new direction in personalized organ repair – once the realm of science fiction, but now yielding incredible discoveries at a rapid pace.



Bonus images for this chapter can be found online at

<http://www.expertconsult.com>

Fig. 16.3 (A) Thumb stump with distraction device. (B) X-ray of bone distraction. (C) New bone filling the gap.



Access the complete reference list online at <http://www.expertconsult.com>

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Repair, grafting, and engineering of cartilage

Wei Liu and Yilin Cao

SYNOPSIS

- Cartilage is one of the most important tissue grafts in plastic surgery and is widely used in auricular reconstruction, rhinoplasty, and facial contouring.
- This chapter introduces the background knowledge and surgical skills required for harvesting cartilage graft and managing donor site tissues.
- Additionally, recent developments in engineered cartilage fabrication and their potential application in plastic surgery are described.

Introduction

Cartilage is a kind of connective tissue which is mainly composed of chondrocytes and their extracellular matrices (ECM) of type II collagen fibers, proteoglycans, and elastic fibers. According to its composition, cartilage can be classified into three types¹: (1) hyaline cartilage; (2) fibrocartilage; and (3) elastic cartilage. Fig. 17.1 shows the histology of the three types of cartilages.

Hyaline cartilage is the most common type of cartilage and can be found in costal, articular, tracheal, and nasal cartilage. With the exception of articular cartilage, the free surface of most hyaline cartilage is covered with perichondrium. In addition to collagen II, hyaline cartilage is rich in glycosaminoglycans and is thus characterized by its stiffness, that permits sustained compressional loading.

Fibrocartilage is composed of bundles of thick collagen fibers along with intervening unicellular islands of cartilage arranged in small chains. Because of this unique structure, fibrocartilage can provide high tensile strength and supporting function and is thus present in areas that are most subject to frequent stress, such as meniscus, intervertebral discs, symphyseal joints, and the joint portion of bone and

tendons/ligaments. In contrast to other cartilage, fibrocartilage also contains type I collagen. In addition, it has moderate amounts of proteoglycan but little glycosaminoglycans.

Elastic cartilage is characterized by its extremely high elasticity because of the presence of abundant amounts of elastic fibers. It is histologically similar to hyaline cartilage but contains many elastic fibers which form an elastic fiber network along with collagen fibers. This unique feature provides great flexibility so that elastic cartilage can withstand repeated bending. It is mainly found in the outer ear structure, and also in the larynx and epiglottis. It is also surrounded with perichondrium.

The perichondrium is a layer of dense irregular connective tissue that consists of two separate layers, an outer fibrous layer and an inner chondrogenic layer. Collagen fibers and fibroblasts constitute the fibrous layer. In contrast, the chondrogenic layer remains partially undifferentiated and is likely to contain mesenchymal stem cells and chondrogenic progenitor cells,^{2,3} which can play a role in cartilage repair and regeneration.

Cartilage is a unique tissue with low metabolic rate due to the sparsity of its cell population and its avascular structure. The glycolytic activity and oxygen consumption of cartilage approaches anaerobic condition and the tissue is nourished by tissue fluid diffusion. Because of this unique feature, cartilage graft is relatively easy to survive when being implanted. In terms of cartilage grafting, Sushruta Samhita in India probably is the first person to perform cartilage grafting in the form of a composite graft.^{4,5} Cartilage graft is widely used for repairing nasal or auricular defects as well as for reconstructing other tissues either as a pure cartilage graft or as a composite graft. According to surgical procedures, cartilage can be transferred either as a free graft or as a microvascular composite graft. Generally, autologous cartilage graft will not have metaplastic changes even being transferred to a different location.⁶ In addition, grafting of free perichondrial tissue is also a common procedure for cartilage reconstruction because

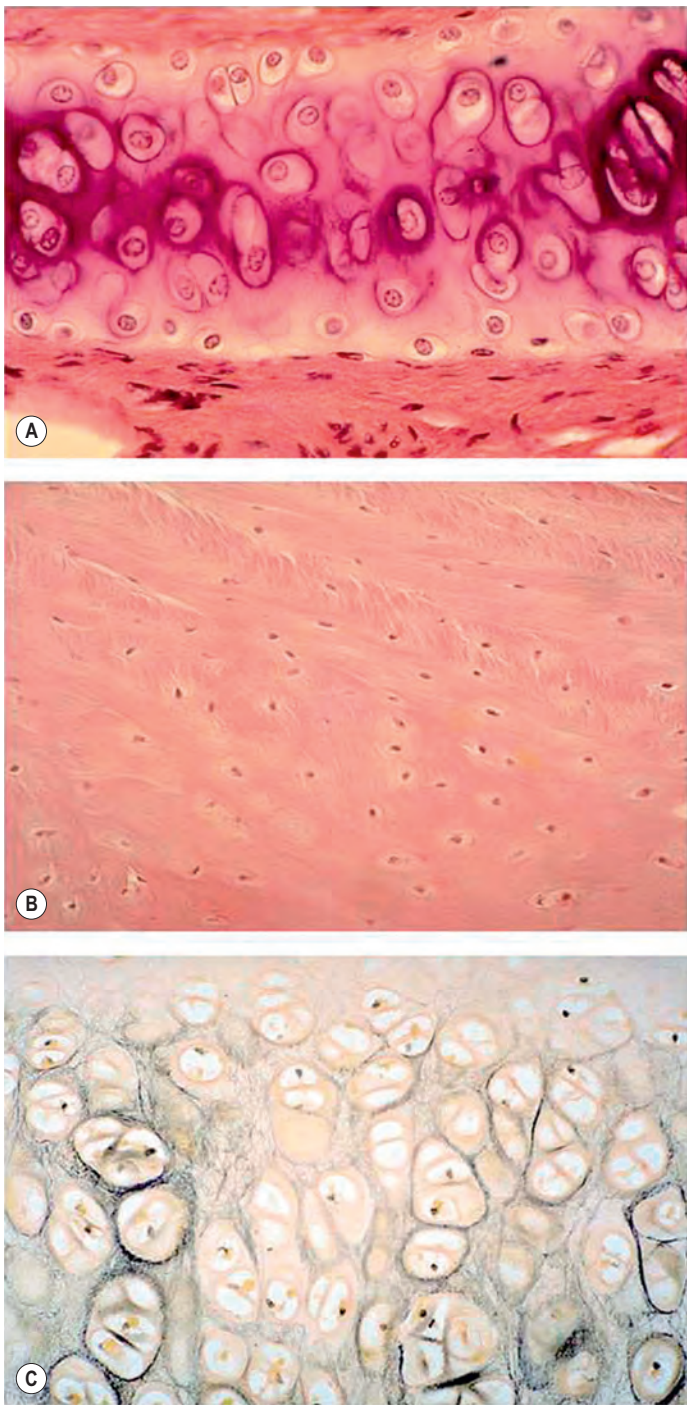


Fig. 17.1 Histology of (A) hyaline cartilage, (B) fibrocartilage, and (C) elastic cartilage (silver staining). (Courtesy of Dr. Roger C. Wagner, Prof. Emeritus of Biological Sciences at University of Delaware and Prof. Fred E. Hossler, East Tennessee State University.)

it has long been observed that perichondrium possesses the ability to regenerate cartilage.⁷

Autologous cartilage grafts and applications⁶

Although cartilage is considered as “immunologically privileged”, and allogeneic cartilage may serve as a potential graft,

autologous cartilage grafting remains the most applicable cartilage graft. Generally, common donor sites for harvesting autologous cartilage grafts include auricular, nasal, and rib cartilage.

Auricular cartilage graft

As an elastic cartilage, auricular cartilage is an ideal graft for transplantation and perhaps is the most versatile of all cartilage grafts because it can be easily fashioned and contoured into different shapes for various uses. Auricular cartilage can be harvested easily under local anesthesia and a significant portion of the concha can be removed without causing donor site deformity.⁶

However, in practice, harvesting of the entire conchal cartilage is likely to cause collapsed conchal bowl, cymba concha, and a horizontally short ear. To overcome this problem, Han *et al.* proposed the surgical procedure that involves: (1) using a postauricular incision to minimize visible scars; (2) harvesting the entire cymba concha and cavum concha separately, with at least 5 mm of the helical crus, leaving a lateral extension as a strut between them, as well as a 2-mm outer rim along the conchal wall; and (3) by using a tie-over bolster dressing that can serve as a mold for the conchal bowl. Fig. 17.2 presents the technique to avoid contour irregularity or deformity after harvesting the maximal amount of conchal cartilage graft.⁸

Auricular cartilage graft is often used as a framework for ear reconstruction or auricular deformity correction, as reported by Brent,⁹ Ono *et al.*,¹⁰ Firmin *et al.*,¹¹ and others. In addition, conchal cartilage can be used as a single-layered graft for nasal, tarsal, and nipple reconstruction.⁶

The other important application of auricular cartilage is to transfer as a composite chondrocutaneous graft for nasal reconstruction. How to manage the donor site of auricular composite graft aesthetically is important for its successful application. Singh and Bartlett have summarized several techniques to deal with the donor site of free auricular composite grafts according to different applications¹²:

- Technique 1: A composite graft that is less than 1 cm can be harvested from the root of the helix and the dog ear is run anteriorly toward the hairline with primary closure of the defect (Fig. 17.3).
- Technique 2: This is designed to close the donor site wound of the composite graft with cartilaginous base of 1–1.5 cm, which is usually needed to repair a wider defect of the alar rim (Fig. 17.4).
- Technique 3: To repair a nasal defect with short vertical dimension (height), the composite graft can be harvested from the anterior aspect of the helical root and the dog ear must be run superiorly and inferiorly. As shown in Fig. 17.5, this technique can provide adequate tissue for nasal reconstruction and an aesthetic closure without disturbing the size of the ear.
- Technique 4: For harvesting grafts with width of 1–1.2 cm from the base of the helix, the defect may be closed primarily by advancing the helical rim forward. The possible resulting overprojection of the ear might be addressed with a postauricular incision and a scaphomastoid suture to match the prominence with the contralateral ear (Fig. 17.6).

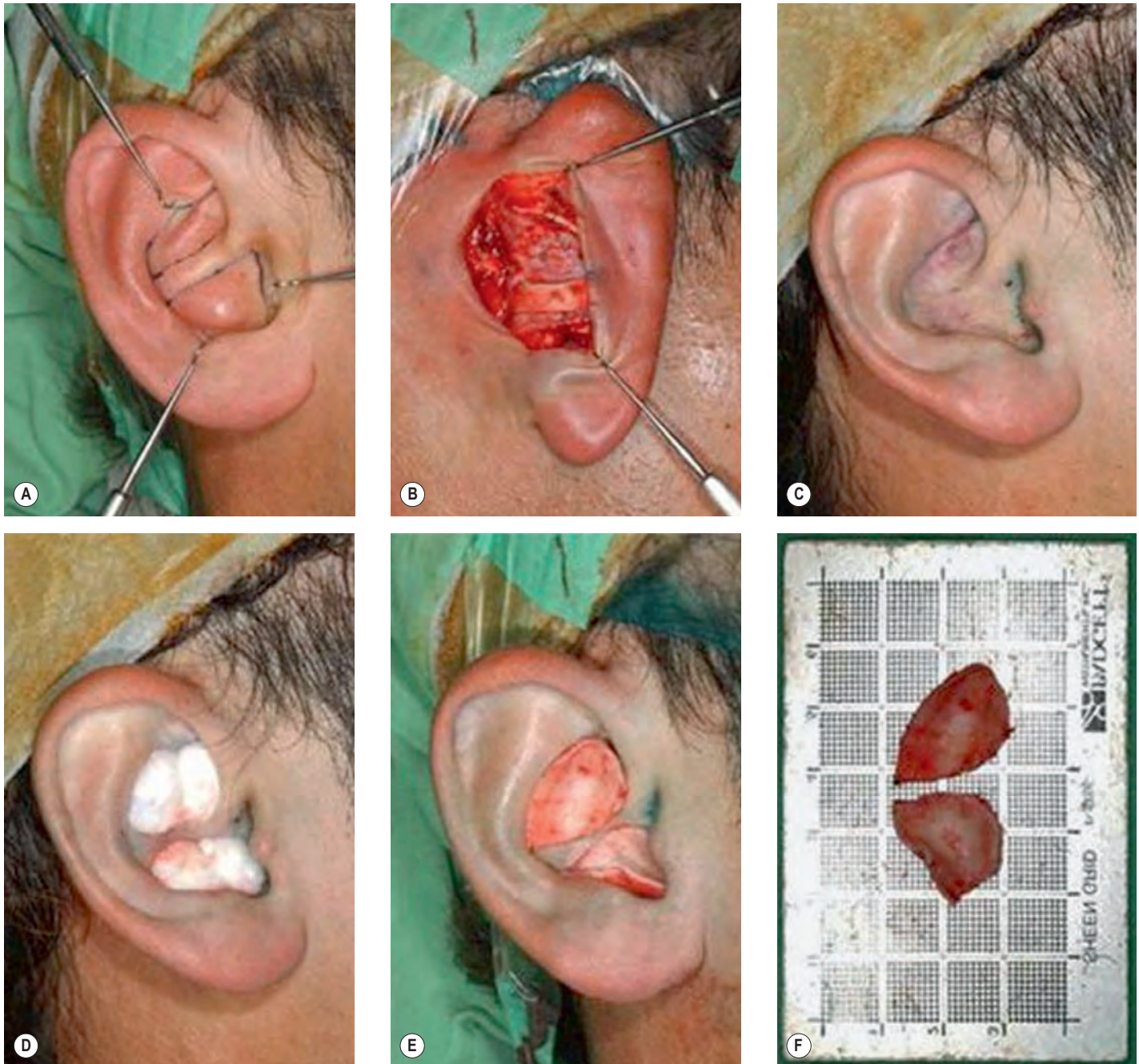


Fig. 17.2 The surgical technique for harvesting the maximal amount of conchal cartilage graft. **(A)** Markings. It was necessary to leave at least 2 mm of the superior outer rim along the conchal wall in order not to cause a noticeable change in the conchal bowl of the donor ear. Note the helical crus with its lateral extension between the cymba concha and cavum concha. **(B)** The entire unit of the cymba concha and cavum concha was removed separately, leaving at least 5 mm of the crus helicus with an extension to prevent collapsing. **(C)** There is almost no external evidence that the large conchal cartilage graft had been removed. **(D)** Two peanut cotton balls were placed into the interstices of the ear and sutured in place with through-and-through 4-0 nylon sutures, which were removed 5 days later. **(E)** The harvested cymba and cavum conchae were placed *in situ* to demonstrate their relationship with the intact helical crus and its lateral extension. **(F)** The surface area was 224.0 mm² at the cymba concha and 247.0 mm² at the cavum concha. (Reproduced from Han K, Kim J, Son D, et al. How to harvest the maximal amount of conchal cartilage grafts. *J Plast Reconstr Aesthet Surg.* 2008;61:1465–1471.)



Fig. 17.3 Technique 1: Harvest of a small composite graft (<1 cm) with primary closure by running the dog ear anteriorly into the hairline. This closure preserves contour of the ear. (*Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. Plast Reconstr Surg. 2007;120:899–908.*)



Fig. 17.4 Technique 2: (A–C) A wider defect of the alar rim requires a larger composite graft from the helical base, as seen by the markings on the ear. (D,E) Closure of the defect is accomplished by running the dog ear anteriorly into the hair line and posteriorly into the triangular fossa. A full-thickness wedge of cartilage must be removed from the triangular fossa to prevent buckling of the ear. (*Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. Plast Reconstr Surg. 2007;120:899–908.*)

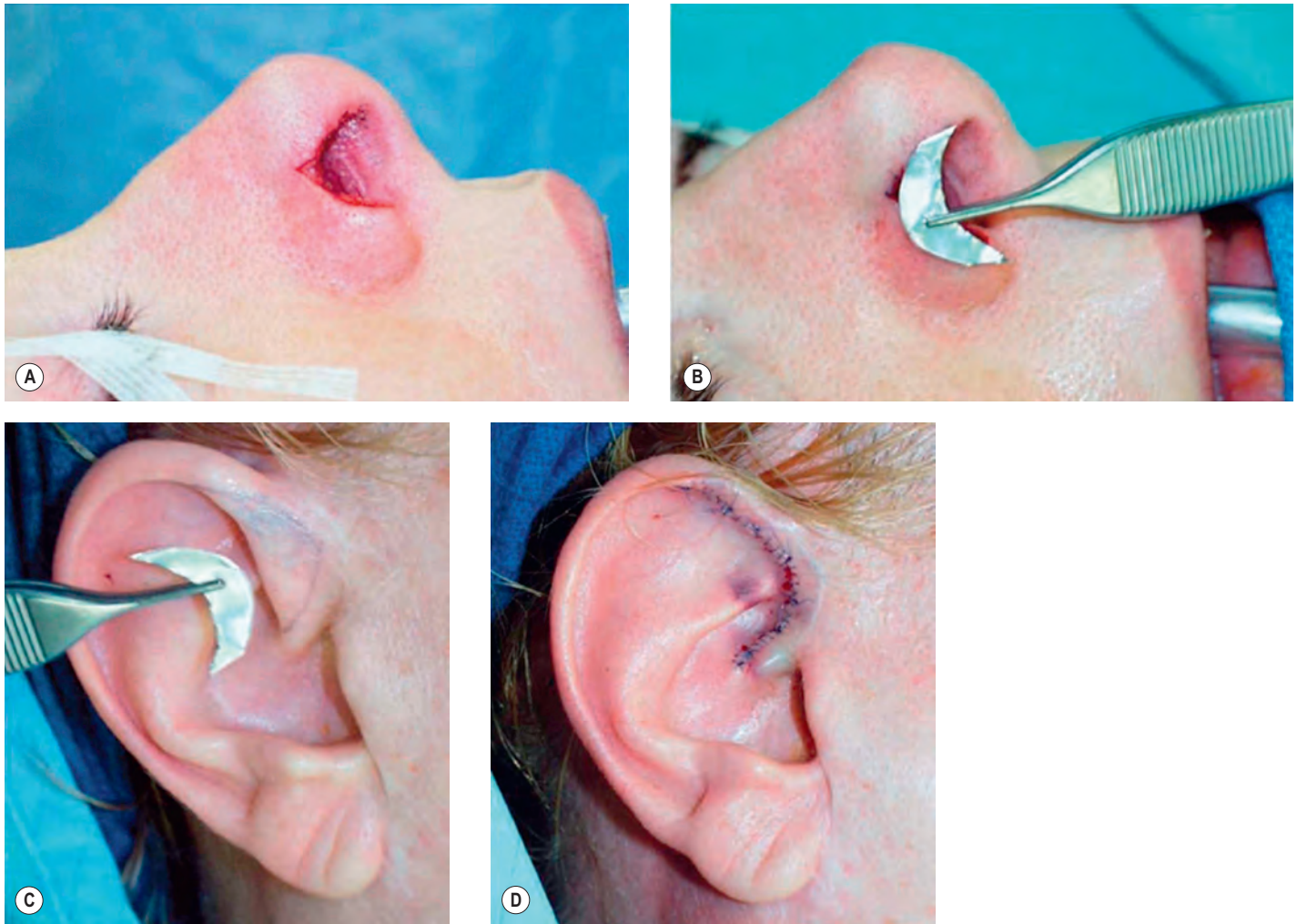


Fig. 17.5 Technique 3: (A, B) The nasal defect is wide but short in its vertical dimension. This allows harvest from the anteroinferior helical rim. (C, D) Primary closure is achieved by running the dog ear superiorly and inferiorly. (Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. *Plast Reconstr Surg.* 2007;120:899–908.)

- Technique 5: After harvesting composite graft wider than 1.5 cm from the base of helix, the closure of such a wound becomes more intricate. A simple helical advancement would result in significant distortion and overprojection (Fig. 17.7). To overcome this, a V-shaped wedge of skin is harvested, but a “half-star” pattern of cartilage at the apex of the V is taken (Fig. 17.8B–E). In addition, a postauricular incision with a scaphomastoid suture is needed. With these procedures, this technique can prevent cupping of the ear with closure (Fig. 17.8F).
- When an extended skin graft component is needed with the composite graft, the composite tissues can be taken either preauricularly or postauricularly, as demonstrated by the markings on Fig. 17.9.

The techniques described above provide simple methods to close the wounds of auricular chondrocutaneous composite grafts primarily with appreciable aesthetic outcome.¹² Other methods of rotational flap or skin graft have also been described in the literature.^{13,14} Importantly, the functional and aesthetic aspects should be well balanced for both the repair

site and donor site when a physician decides to harvest an auricular composite chondrocutaneous graft of a particular size and shape.

One concern for the clinical application of free auricular composite grafts is their limited size due to the lack of immediate blood supply after transplantation. In contrast, microvascularly transferred auricular composite grafts can overcome this limit and are particularly useful when repairing large nasal defects. Zhang *et al.* have recently reviewed their experiences of surgical treatment of large nasal defects with vascularized preauricular and helical rim flaps based on the superficial temporal vessels in 63 clinical cases. The repaired deformities include unilateral alar defect, alar and side wall defects, tip and columellar defects, entire lower third of the nose missing, and composite defects involving cheek and maxilla. The total flap survival rate reached 97%. The results demonstrate that such an approach, using vascularized preauricular and helical rim flaps, is a reliable method for reconstructing nasal defects.¹⁵ Fig. 17.10 demonstrates the surgical technique for repairing an alar lobule defect with vascularized helical rim composite tissue and preauricular skin.¹⁵



Fig. 17.6 Technique 4: (A, B) Inset of graft and aesthetic outcomes of nasal reconstruction and (C) the auricular donor site in comparison with (D) the contralateral ear. (Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. *Plast Reconstr Surg.* 2007;120:899–908.)



Fig. 17.7 (A–C) With harvest of a small (1–1.2 cm) composite graft, closure can be achieved by helical rim advancement. However, overprojection of the ear may result, as seen in this series of photographs. (Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. *Plast Reconstr Surg.* 2007;120:899–908.)

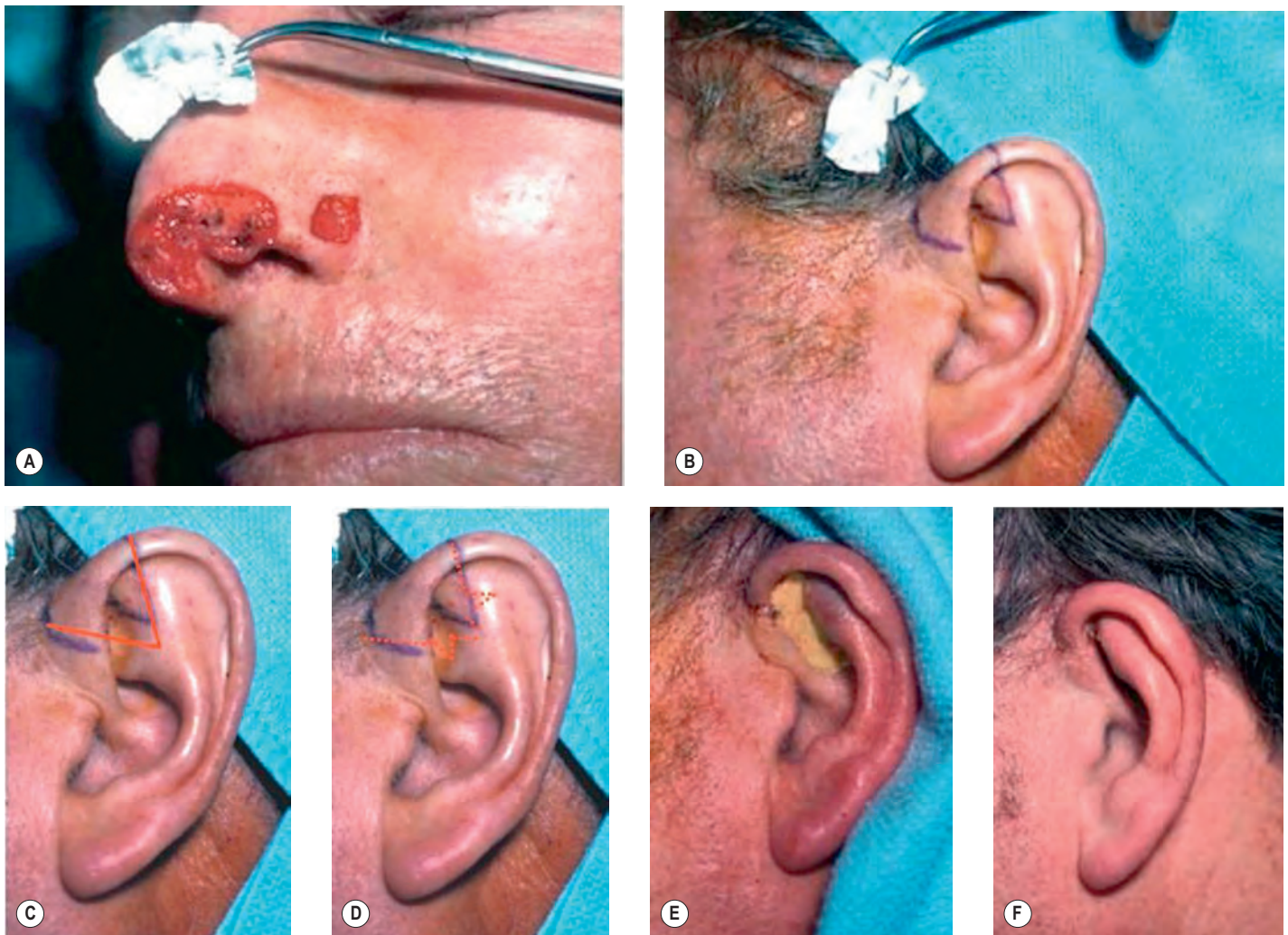


Fig. 17.8 Technique 5: (A,B) This nasal defect requires a larger composite graft with a width of 1.8 cm. The harvest site on the auricle is demonstrated by the purple lines. (C–E) To overcome distortion and overprojection resulting from tissue harvest, closure for this size auricular defect involves a V-shaped wedge of skin and a half-star pattern of cartilage excision at the apex of the V. The solid lines indicate skin incision and the dotted star pattern demonstrates cartilaginous incisions. In addition, a postauricular incision with a scaphomastoid suture is performed. (F) This technique of wound closure prevents the cupping of the ear and relatively normal shape and projection of the ear are maintained after the closure. (Modified from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. *Plast Reconstr Surg.* 2007;120:899–908.)

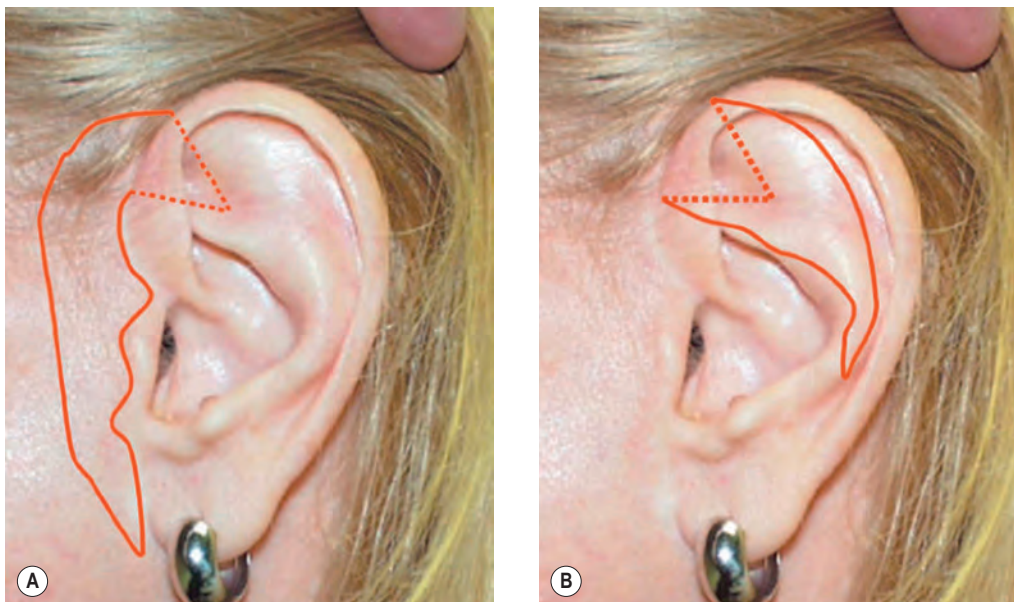


Fig. 17.9 Occasionally, an extended skin graft is needed in addition to the composite graft for reconstruction of nasal defects. (A) The solid lines indicate skin incisions and the dotted line indicates a cartilaginous incision. (B) The solid lines represent the harvest of a postauricular full-thickness skin graft. (Reproduced from Singh DJ, Bartlett SP. Aesthetic management of the ear as a donor site. *Plast Reconstr Surg.* 2007;120:899–908.)

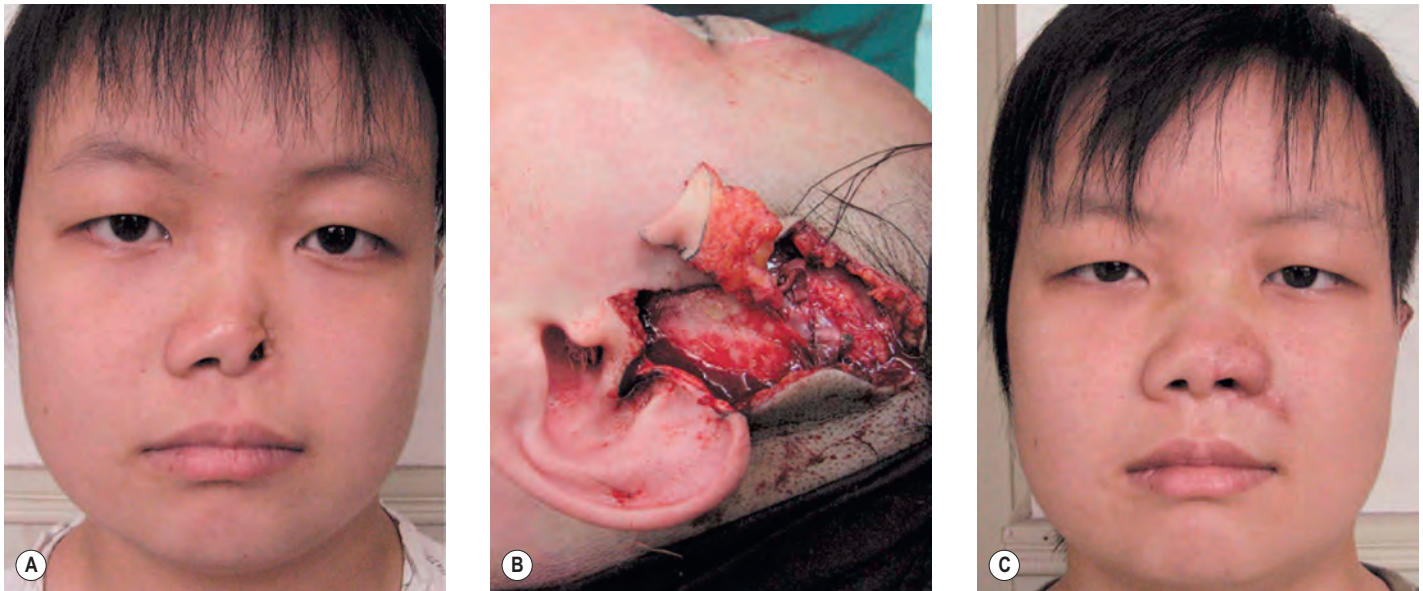


Fig. 17.10 A 17-year-old female with a deformity of the left alar lobule after laser treatment of a hemangioma. An ipsilateral reverse-flow flap consisting of both the helical rim and the preauricular skin (2.2×1.8 cm) was used. The anastomosis was made to the proximal end of the superficial temporal vessels by means of 11-cm vascular grafts from the descending branch of the lateral circumflex vessels. (A) Preoperative and (B) intraoperative views of the harvest of a reverse-flow flap based on the distal superficial temporal vessels. (C) Postoperative view at 3-month follow-up. (Reproduced from Zhang YX, Yang J, Wang D, et al. Extended applications of vascularized preauricular and helical rim flaps in reconstruction of nasal defects. *Plast Reconstr Surg.* 2008;121:1589–1597.)

Nasal cartilage graft

Although limited in its available amount, nasal cartilage has been employed as a composite chondromucosal graft for eyelid reconstruction. Septal cartilage is an important source of nasal cartilage graft. As reported by Murrell, the septal cartilage can be accessed via a hemitransfixion incision with dissection around the caudal margin of the quadrangular cartilage. After both sides of mucoperichondrium are raised, the septal cartilage can be harvested.¹⁶ Importantly, as shown in Fig. 17.11, an L-shaped septal strut should be preserved to give nasal support and avoid nasal collapse.^{6,16} Nevertheless, the amount of L-shaped strut cartilage necessary to provide good support can vary greatly depending on the strength, thickness, and dimensions of the nasal septum and other nasal tissues (i.e., upper lateral cartilages, lower lateral cartilages, nasal bones).¹⁶ As early as 1962, Millard published his work of repairing eyelid defects with a chondromucosal graft harvested from nasal septum. Later, Mustardé also described the technique in the book *Repair and Reconstruction in the Orbital Region*.⁶

The other region available for harvesting nasal chondromucosal graft is the upper lateral nasal cartilage, as reported by Tessier in 1979.⁶ In clinical practice, repairing a large defect of the upper eyelid is always a challenge. Scuderi and colleagues have developed a surgical technique to address such a concern. In their report, a pedicled nasal chondromucosal flap was designed along the lateral nasal wall based on the terminal branch of the dorsal nasal artery. The flap includes the subcutaneous tissues down to the periosteum and the cranial portion of the upper lateral cartilage. It can be harvested either unilaterally or contralaterally and a skin graft is applied for cutaneous coverage. In their reported 15 patients, the flap was viable in every patient and satisfactory functional recovery was achieved, indicating that this one-stage procedure can reconstruct a thin and mobile eyelid.¹⁷

Fig. 17.12 demonstrates its design and surgical procedure as well as its clinical outcome.¹⁷ In addition to eyelid repair, septal cartilage graft has been used for dorsal augmentation,¹⁶ tracheal repair,¹⁸ and extended septal graft for controlling the projection shape of nose tip.¹⁹

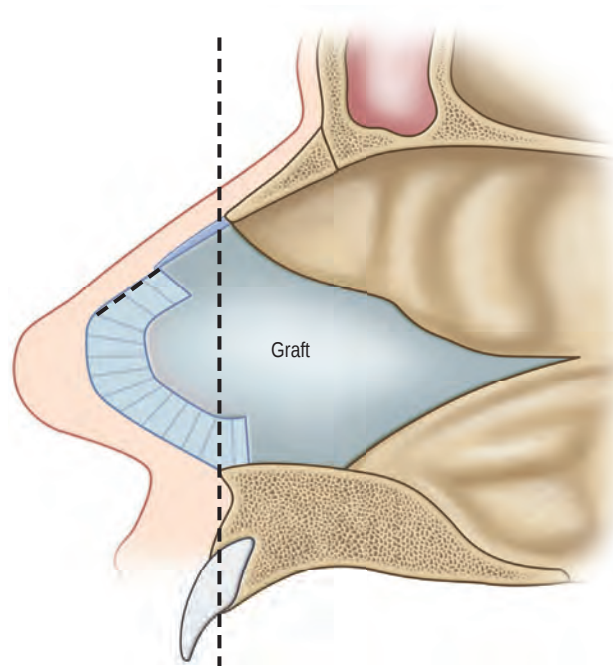


Fig. 17.11 Harvest of nasal septal cartilage graft. It is important to keep the L-shaped strut cartilage (shown in stripes) to provide nasal support. The area of septum that attaches to the upper lateral cartilages should also be preserved. Generally, nonsupportive quadrangular cartilage, which is pictured posterior to the dashed vertical line, can be harvested freely. (Reproduced and modified from Murrell GL. Dorsal augmentation with septal cartilage. *Semin Plast Surg.* 2008;22:124–135.)

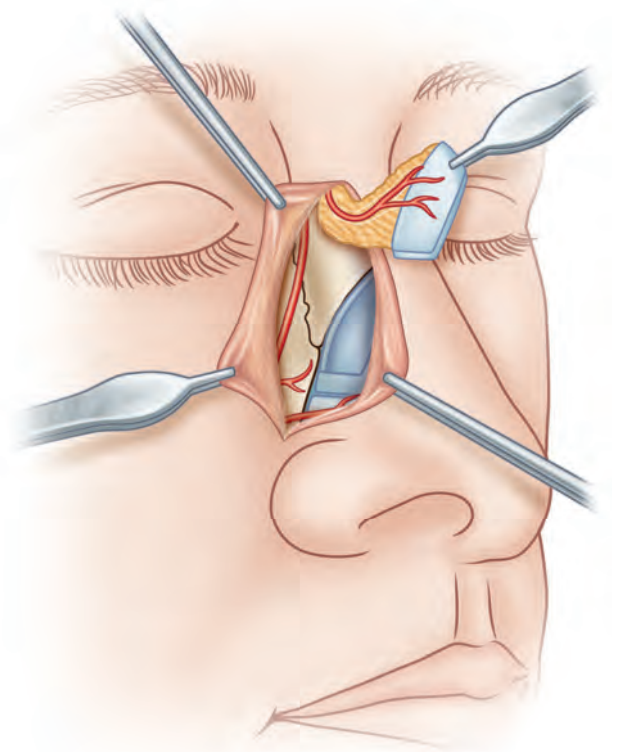
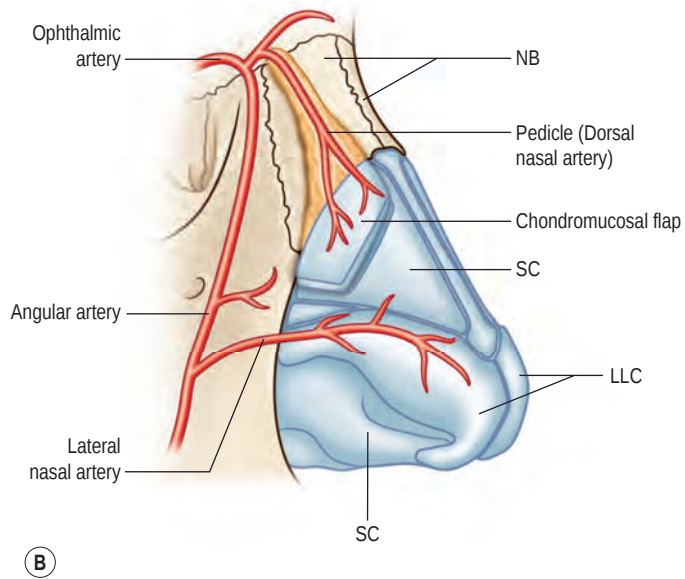
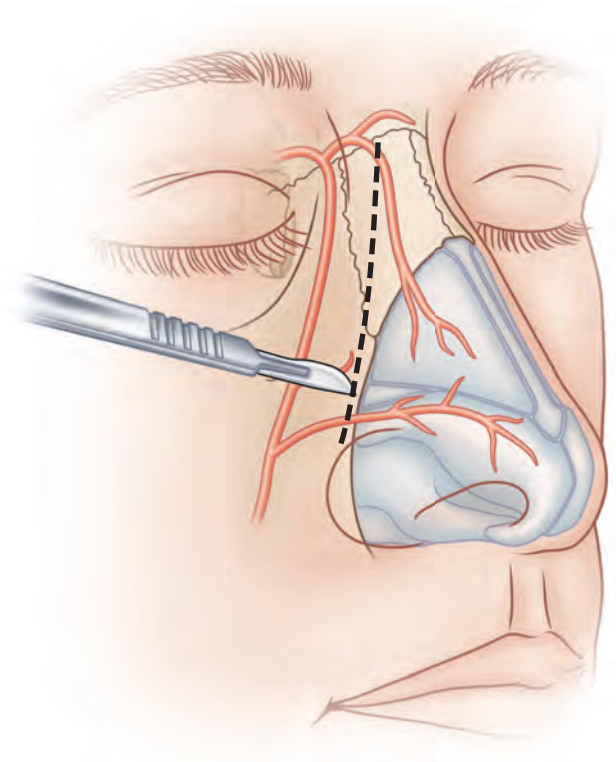
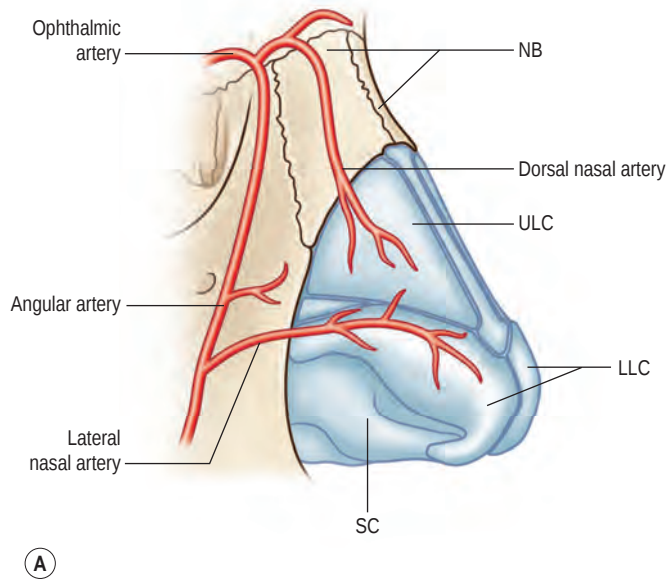


Fig. 17.12 Schematic illustration of the design and procedure of a pedicled nasal chondromucosal flap for upper eyelid reconstruction. **(A)** Preoperative markings for harvest of the upper lateral cartilage (ULC) in the nasal chondromucosal flap, which is based on the lateral terminal branch of the dorsal nasal artery. NB, nasal bone; LLC, lower lateral cartilage; SC, septal cartilage. **(B)** After skin incision and undermining, the flap is raised after a portion of the upper lateral cartilage is harvested.

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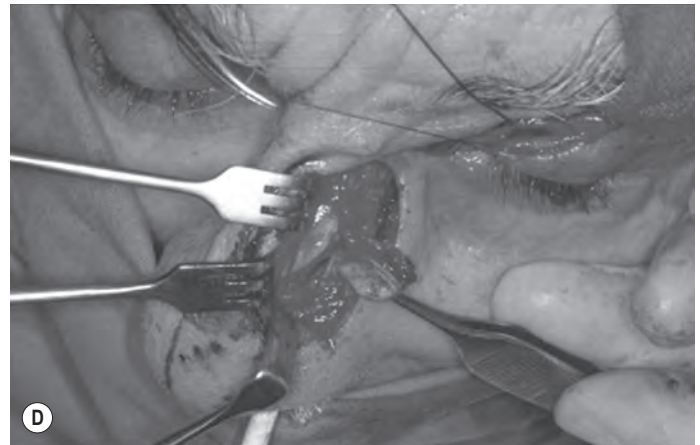


Fig. 17.12, cont'd (C) Clinical outcome of upper eyelid defect repaired with pedicled nasal chondromucosal flap. Carcinoma of the upper eyelid. **(D)** Harvest of the nasal chondromucosal flap. **(E,F)** One-year postoperative result after reconstruction with the nasal chondromucosal flap. (Reprinted and modified from Scuderi N, Ribuffo D, Chiummariello S. Total and subtotal upper eyelid reconstruction with the nasal chondromucosal flap: a 10-year experience. *Plast Reconstr Surg.* 2005;115:1259–1265.)

Rib cartilage graft

Costal cartilage may serve as the best donor site for cartilage graft in terms of available tissue amount and mechanical strength. The autologous rib cartilage can be virtually contoured into any desired shape and it can retain form and bulk after implantation if basic surgical principles are followed.⁶ The costal cartilage graft is often used as a cartilage framework for total ear reconstruction. Tanzer,²⁰ Thomson *et al.*,²¹ and Brent²² have respectively described the technique to harvest costal cartilage to construct auricular framework. In the procedure, the synchondrosis of the sixth and seventh cartilages as well as the eighth costal cartilage is harvested, usually along with the perichondrium.^{20–23} In contrast, Nagata's method for total auricular reconstruction requires the harvest of four costal cartilages in the first-stage operation and one or two costal cartilages for the second-stage operation.^{24–28} Fig. 17.13 is a schematic illustration of the harvest of rib cartilage designed for ear reconstruction or chin contouring.²⁹

In clinical practice, harvest of costal cartilage can be associated with donor site morbidity. Uppal *et al.* have reported their investigation on morbidity associated with the harvest of costal cartilage in 42 patients who underwent ear reconstruction. The commonest complaints included pain and clicking of the chest wall, which usually peaked in the first

week postsurgery and gradually diminished over 3 months. The other problems were scar and chest wall deformity.³⁰ Among them, the most challenging problems are pneumothorax during the surgical procedure and resulting abnormal chest wall contour. This is particularly true for Nagata's

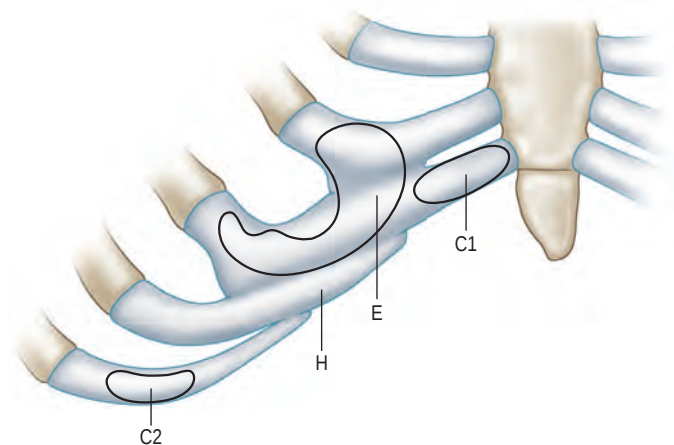


Fig. 17.13 Donor site for costal cartilage grafts in auricular framework and chin graft construction. E, ear base block; H, helix; C1, chin graft, first layer; C2, chin graft, second layer. (Reproduced and modified from Brent B. *Repair and grafting of cartilage and perichondrium.* In: McCarthy JC (ed). *Plastic Surgery.* Philadelphia: WB Saunders; 1990:559–582.)

method, which requires more and extra cartilage grafts for auricular reconstruction.^{24–28}

To address this concern, Kawanabe and Nagata developed a new method for harvesting rib cartilage to avoid intra-operative and postoperative complications and problems. In this modified procedure, the costal cartilages were harvested *en bloc* with the perichondrium left completely intact at the donor site. In addition, after the fabrication of the auricular cartilage frame, the remaining costal cartilage was cut into small blocks that acted as spacers to fill the dead space formed in the perichondrial pocket. The retained perichondrium not only helps to avoid the injury of pleura, but may also promote cartilage regeneration because of the presence of chondrogenic stem cells.^{2,3} In an investigation of 270 cases of total auricular reconstruction performed using Nagata's method and the new method of rib cartilage harvesting, the incidence of infection and pneumothorax was reduced to less than 1%. More importantly, there were no postoperative chest wall deformities when costal cartilage was harvested with this new technique.³¹ Interestingly, a follow-up study revealed that returned hyaline cartilages were mixed with fibrocartilage with visible margins at 6 months postsurgery. Twelve months after the first-stage operation, homogeneous hyaline cartilage was observed histologically, and the regenerated cartilages were similar to native costal cartilages in their hardness, which enabled the second harvest.³² Fig. 17.14 gives a schematic illustration of harvesting costal cartilage with the new method of retaining perichondrium and returning the remaining costal cartilage to the donor site.³¹

Modification of previously established methods of making auricular framework is also considered as an alternative option to avoid harvesting extra cartilage and thus help to prevent chest wall deformity. As an example, Chin *et al.* recently reported several modifications of auricular framework which required less cartilage graft and meanwhile could also generate individualized and harmonious ear frameworks to meet the need for satisfactory three-dimensional (3D) outline of a reconstructed auricle.³³ The framework may consist of the helix, the base frame, the Y-shaped antihelical complex, and the tragus attached to an additional cartilaginous cube depending on individualized need (Fig. 17.15). In addition, bone cement is used as the support material during the ear elevation stage, and therefore extracostal cartilage harvesting became unnecessary.³⁴ Fig. 17.16 demonstrates the clinical outcome of reconstructed ear with modified frameworks based on the individualized 3D auricle structures.³³

In addition to auricular reconstruction, rib cartilage graft also has other applications, including reconstruction of significant saddle-nose deformity,³⁵ treatment of maxillonasal dysplasia (Binder's syndrome),³⁶ nipple reconstruction,³⁷ for septorhinoplasty,³⁸ and in tracheal reconstruction.³⁹

Autologous perichondrial graft

In 1959, Lester first reported the potential of neocartilage formation by transplanted perichondrium.⁴⁰ This phenomenon has also been observed by others.^{41–44} Despite the enthusiasm and optimism derived from the pioneering observations, the clinical application of perichondrial grafts for cartilage regeneration remains limited to certain conditions, such as the reconstruction of degenerated knee joint cartilages. The

potential causes limiting its application include the technique of harvest, the oxygenation of the recipient bed, and the presence of chondroprogenitors at the recipient site, which can all have an influence on the composition of the new tissue.⁴⁵ With proper microenvironments, perichondrium-mediated cartilage regeneration remains possible, as revealed by experimental studies. For example, Sari *et al.* reported neocartilage formation in a folded-ear perichondrium at 6 weeks postimplantation under the abdominal muscle in rabbit.⁴⁵

One of the major clinical applications is for joint repair. As early as 1975, Engkvist *et al.* reported a pilot experimental study of regenerating articular cartilage of cavitas glenoidalis by transplanting ear perichondrium in a rabbit model. Further, clinical trials were formed in 5 cases of arthritis patients. After removal of the degenerated cartilage, rib perichondrium was grafted and articular cartilage regeneration took place.⁴⁶ Following the initial trials, there were some reports of the application of perichondrium graft for clinical repair of human knee joint articular cartilage,^{47,48} but there were few on repairing articular cartilage of human digits.⁴⁹ Instead, transplantation of costal osteochondral grafts became the major tissue graft for functional restoration of injured digital articular cartilage.^{50,51}

The other important clinical application might be nasal reconstruction either as a perichondrium graft or as a perichondrocutaneous graft. Recently, Boccieri and Marianetti reported the application of perichondrium graft for nasal surgery. Because of its thinness and malleability, perichondrium is particularly suitable for covering every part of the cartilaginous graft, and is easy to fold into various layers if greater thickness is required in filling certain areas and therefore is commonly used in secondary rhinoplasty.^{52,53} Fig. 17.17 demonstrates the surgical procedure of nasal tip reconstruction with auricular perichondrium.⁵²

In addition, perichondrocutaneous graft is a common graft type. Brent and Ott reported the graft and proposed its application in reconstructive facial surgery in 1978.⁵⁴ The donor source for the graft should be restricted to concha in order to prevent deformity.⁶ This graft has wide applications. It has been reported to be used for facial reconstruction,^{55,56} for reconstruction of nasal defect,^{57,58} for auricular defect repair,⁵⁹ and repairing ectropion.⁶⁰ Overall, although both perichondrium and perichondrocutaneous grafts have been widely used for clinical repair of tissue defect, there remains no solid clinical evidence to support the theory that transplanted perichondrium is able to regenerate a significant amount of cartilage tissue.

Cartilage engineering

Introduction and basic principle

Cartilage probably is one of the most commonly used tissue grafts in plastic surgery and has been employed in auricular reconstruction, rhinoplasty, and other surgical procedures, as described above. However, autologous cartilage graft is limited in its available amount and tissue harvest may cause donor site morbidity.

Tissue engineering is a new biotechnology developed from the late 1980s and early 1990s, which aims to repair and regenerate human tissue via an engineering approach

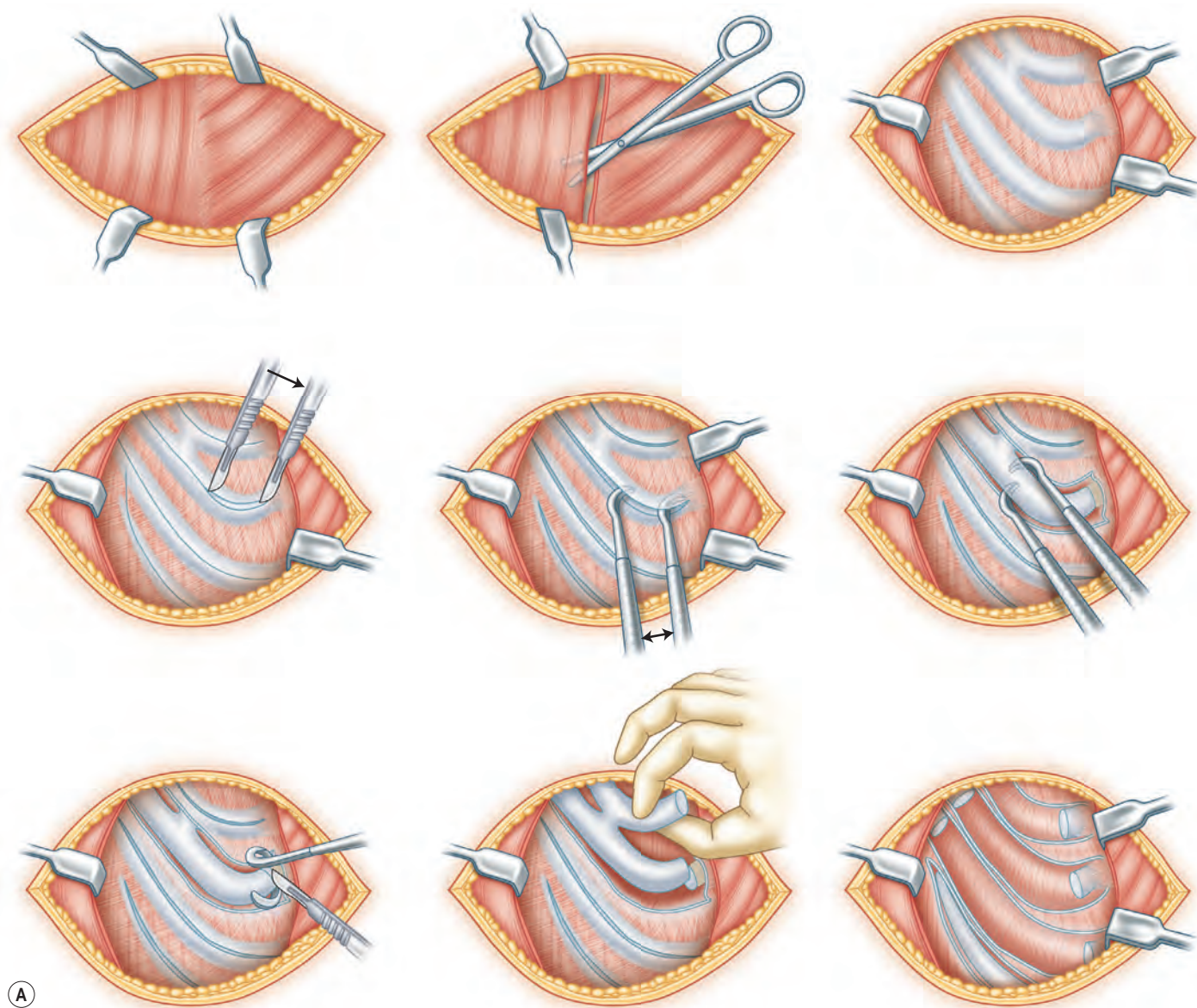


Fig. 17.14 (A) Schematic illustration of the new method of costal cartilage harvest. (Top, left) The muscular fascia of the rectus abdominis muscle and the external oblique muscle are exposed. (Top, center) A longitudinal incision is made between the rectus abdominis muscle and the external oblique muscle with delicate dissecting scissors. (Top, right) The perichondrium is completely exposed. (Center, left) The line of incision is marked in the center of the costal cartilage, and, taking special care not to injure or damage the cartilage, the incision is made with a scalpel. (Center, center) The anterior surface of the perichondrium is first undermined with an elevator. (Center, right) The undermining of the posterior surface of the perichondrium requires extreme caution because the risk of pneumothorax exists; therefore, the tip of the elevator is placed on the cartilage or must face the cartilage to avoid accidental puncture of the thoracic wall. The approximately 1 cm of periosteum at the costochondral junction is undermined for easier harvest of the costal cartilage. (Bottom, left) A Doyen rib raspatory is inserted underneath the undermined costal cartilage between the cartilage and the perichondrium at the costochondral junction. The costal cartilage is excised with a scalpel and the costochondral junction is to be left behind at the donor site. (Bottom, center) Harvesting of the costal cartilages is easier if the sixth and seventh costal cartilages are harvested from the side of the costochondral junction instead of the sternal side. (Bottom, right) The appearance of the donor site immediately after the harvest of the costal cartilages. The perichondrium is left completely intact at the donor site.

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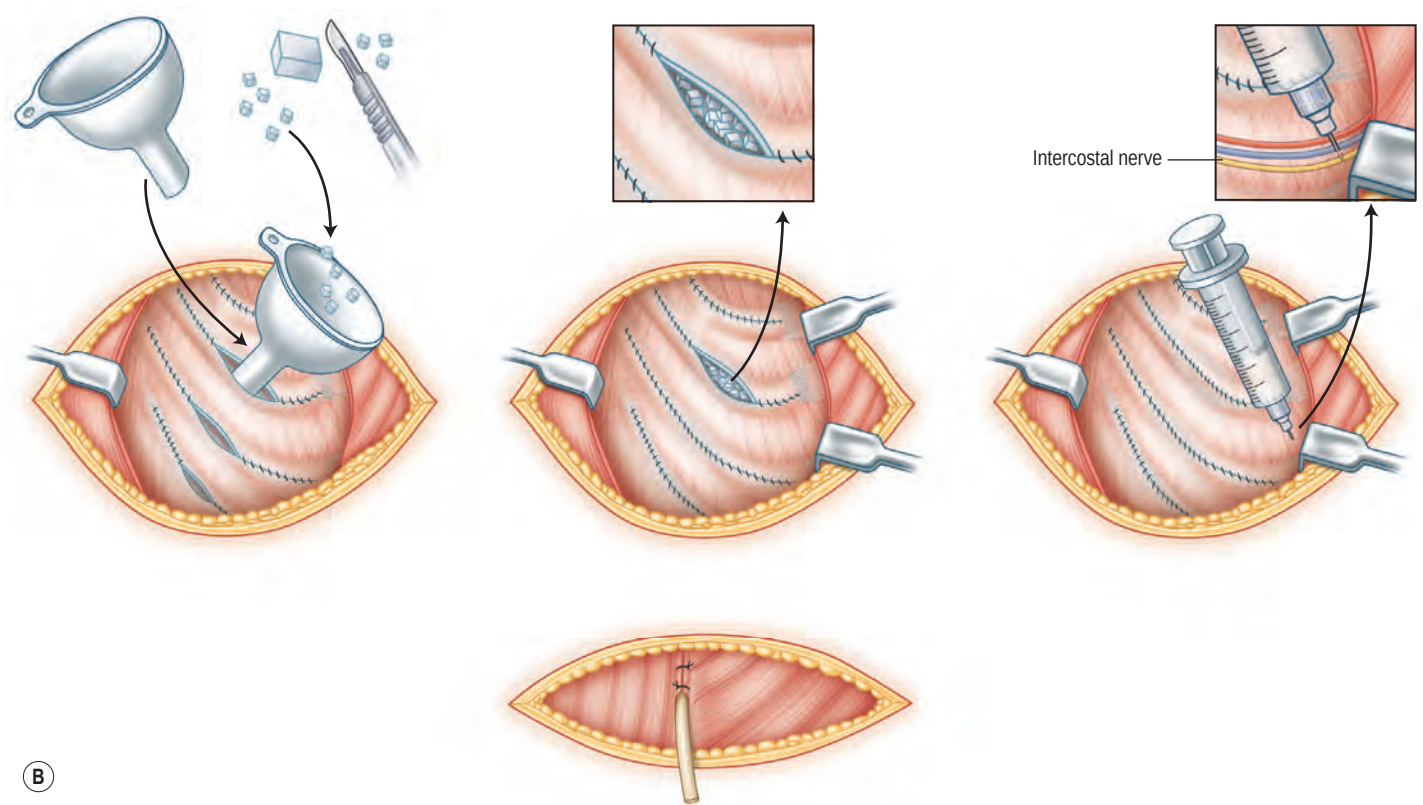


Fig. 17.14, cont'd (B) (Top, left) The perichondrium is sutured with 4-0 nylon at 5-mm intervals with the exception of one area for the return of the remaining costal cartilage after fabrication of the three-dimensional costal cartilage framework, which is cut into 2–3-mm blocks. A small funnel is placed in the unsutured opening of the perichondrium for returning the cut cartilage blocks. (Top, center) The appearance after the return of cut cartilage blocks. The cartilage blocks are visible at the opening of the perichondrium. (Top, right) Intercostal nerve block is performed for reducing postoperative pain with 0.25% Marcaine under direct vision. A total of 5 mL is administered per rib. (Bottom) The muscle and muscular fascia are sutured with 4-0 nylon and a Penrose drain is placed under the muscular layer. (Reproduced from Kawanabe Y, Nagata S. A new method of costal cartilage harvest for total auricular reconstruction: part I. Avoidance and prevention of intraoperative and postoperative complications and problems. *Plast Reconstr Surg.* 2006;117:2011–2018.)

to produce autologous tissue. Actually, cartilage is closely related to the development of tissue engineering because it was used as a tissue target to prove the basic principle.^{61,62} Interestingly, the success in the engineering of human ear-shaped cartilage in a nude mouse model vividly revealed that this tissue-engineering technique has great potential in plastic surgery for tissue repair and reconstruction.⁶³

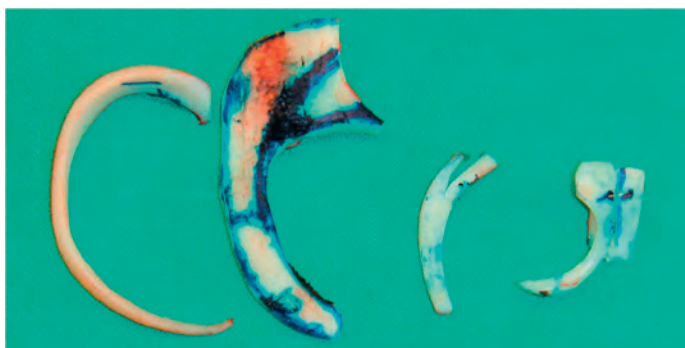


Fig. 17.15 The modified rib cartilage framework may contain these parts to provide prominent structures. From left to right, the helix, the base frame, the Y-shaped antihelical complex, and the tragus attached to an additional cartilaginous cube. (Reproduced from Chin W, Zhang R, Zhang Q, et al. Modifications of three-dimensional costal cartilage framework grafting in auricular reconstruction for microtia. *Plast Reconstr Surg.* 2009;124:1940–1946.)

As outlined by Stock and Vacanti,⁶⁴ the basic concept of tissue engineering includes a scaffold that provides an architecture on which seeded cells can organize and develop into the desired organ or tissue prior to implantation. The scaffold provides an initial biomechanical profile for the replacement tissue until the cells produce an adequate ECM. During the formation, deposition, and organization of the newly generated matrix, the scaffold is either degraded or metabolized, eventually leading to a vital organ or tissue that restores, maintains, or improves tissue function.

Generally, the tissue-engineering process involves three major components: (1) seed cells: the component for matrix production, deposition, and tissue formation; (2) scaffold: the substance that provides a 3D construct for cells to reside, proliferate, and produce matrix; (3) tissue formation environment: after being seeded on the scaffold, cells start to grow and produce and deposit ECMs on the scaffold. In a proper environment, with gradual degradation of the scaffold, cell proliferation, matrix production, and proper tissue remodeling, an engineered tissue gradually forms and becomes mature.

In the past 20 years, tremendous progress has been made in basic and applied research of cartilage engineering, including the search for different biomaterials as scaffolds, seeking different cell sources and chondrogenic induction of stem cells as well as advances in the techniques of cartilage tissue formation, such as *in vitro* reconstruction of cartilage tissue. Among

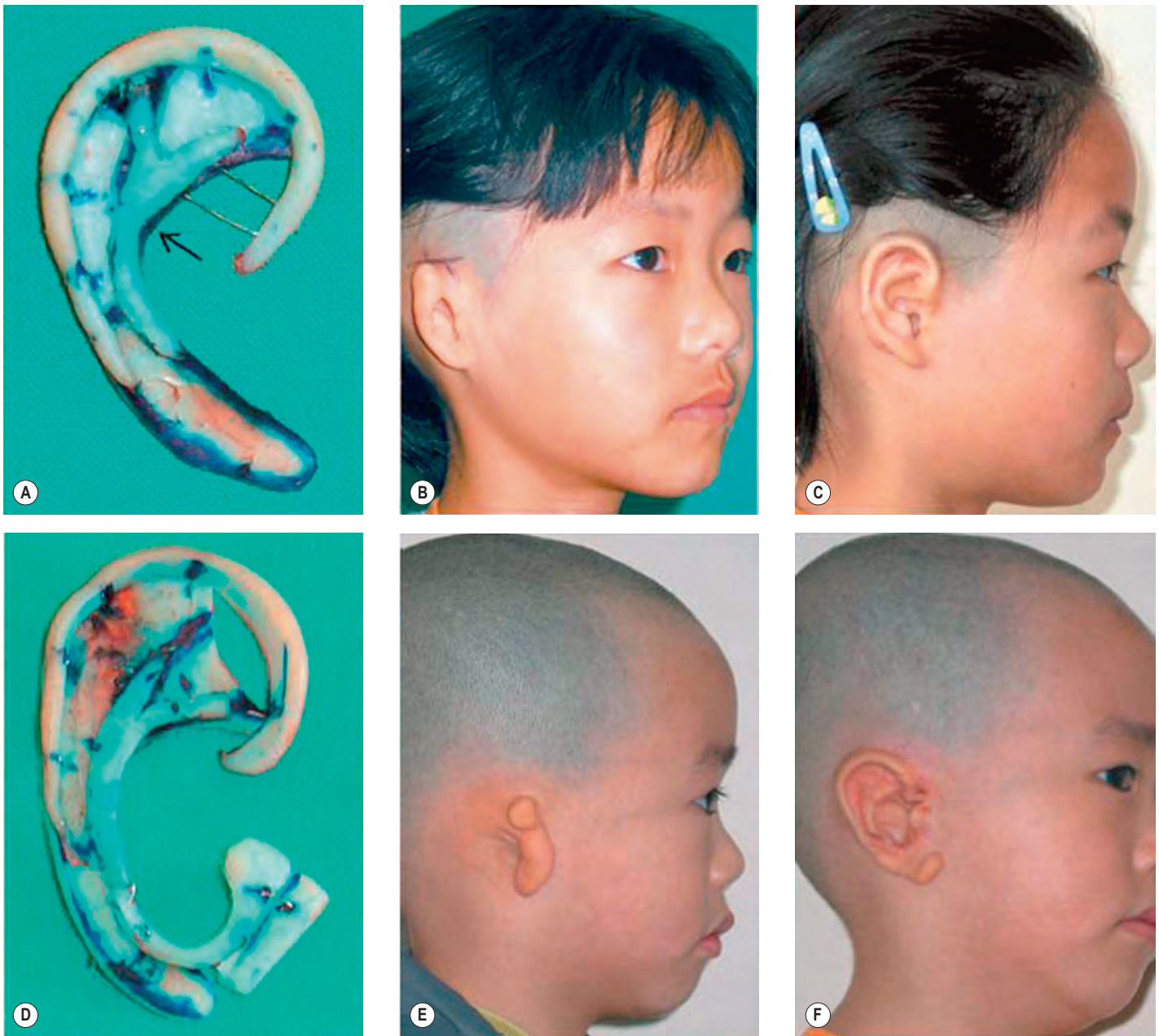


Fig. 17.16 Auricular reconstruction with modified frameworks. (A–C) A 7-year-old girl presented with congenital microtia. (A) The three-dimensional framework used: the arrow indicates the Y-shaped antihelical complex attached on the base frame. (B) Preoperative oblique view of conchal-type microtia. (C) Close-up appearance of the reconstructed auricle 8 months after grafting of the framework. (D–F) A 6-year-old boy presented with congenital microtia. (D) The completed costal framework with Y-shaped antihelical complex and the tragus attached to an additional cartilaginous cube. (E) Preoperative lateral view of sausage-type microtia. (F) Postoperative oblique view, 3 months after grafting of the framework. (Modified from Chin W, Zhang R, Zhang Q, et al. *Modifications of three-dimensional costal cartilage framework grafting in auricular reconstruction for microtia*. *Plast Reconstr Surg*. 2009;124:1940–1946.)

them, some have already revealed the great potential in plastic surgery, for example, auricular reconstruction, rhinoplasty, and facial contouring. The following gives a few examples of generation techniques and the results of engineered cartilages that may potentially be used for cartilage repair and reconstruction.

Engineering of auricular cartilage

An important achievement in cartilage engineering research is the development of the technique that enables generation of a human ear-shaped cartilage, because it vividly reveals

the application potential in plastic surgery. The procedure is described below to provide an example of translational research of cartilage engineering.⁶³

To generate a human ear-shaped cartilage, selection of seed cell, scaffold materials, and an animal model should be determined according to the principle. In this study, chondrocytes derived from calf cartilage, polyglycolic acid (PGA), unwoven fibers, and a nude mouse model served as the basic components to construct the cartilage.

To isolate the cells, cartilage fragments were first harvested from the articular surface of glenohumeral and humeroulnar joints and then subjected to collagenase digestion (3 mg/mL)

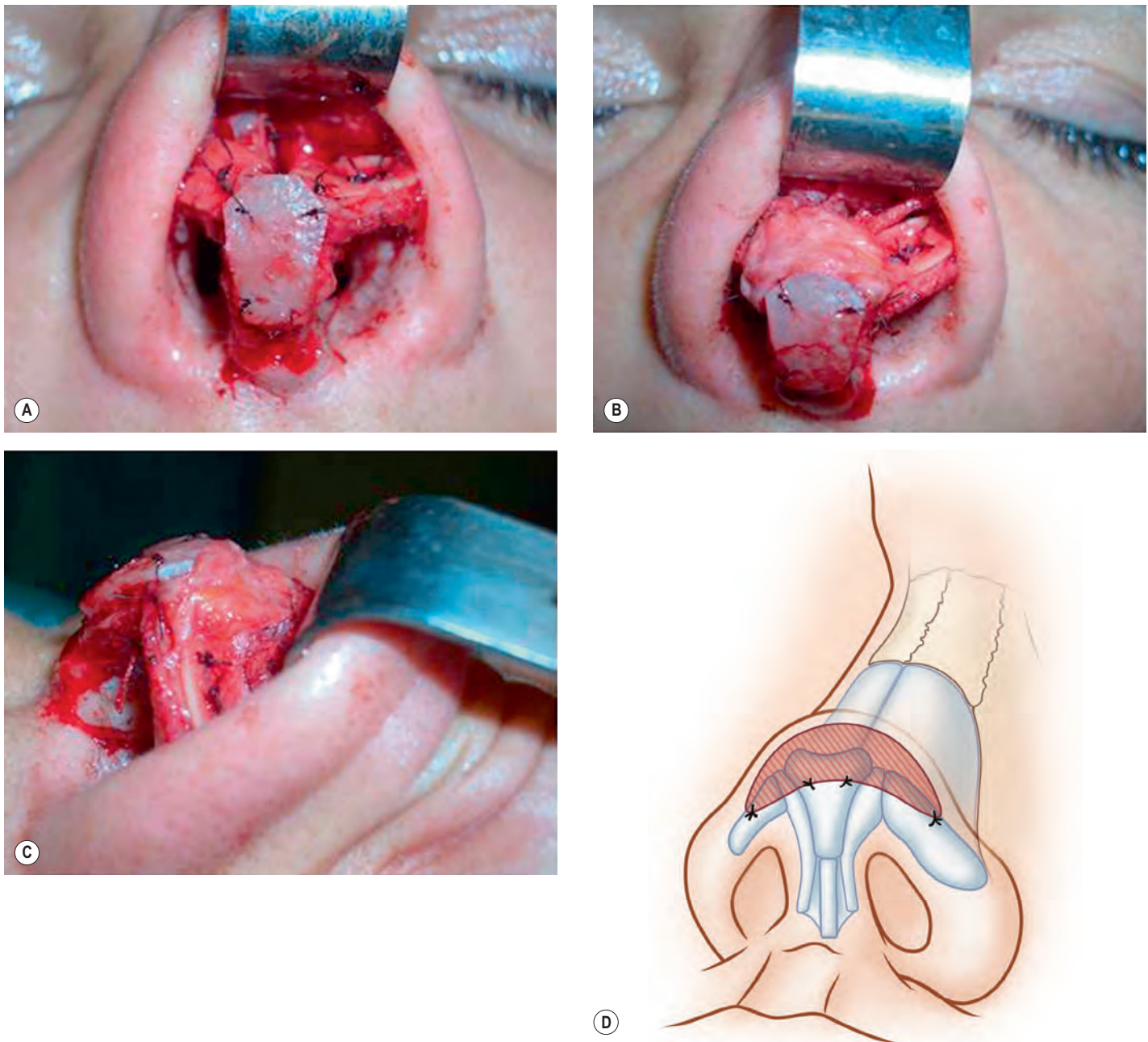


Fig. 17.17 (A) Reconstruction of the nasal tip with lateral crural and shield grafts (Sheen-type) harvested from the cartilage of the auricular concha. (B) Graft of the perichondrium stretched over and secured to cartilaginous grafts to make the contours smooth and disguise tip grafts. (C) Lateral view of the same graft. (D) Schematic illustration of the perichondrium graft positioning and fixation. The presence of numerous grafts inevitably leads to sharp ridges and irregularities in the cartilaginous contour that can be eliminated by means of the perichondrium graft. (Modified from Boccieri A, Marianetti TM. Perichondrium graft: harvesting and indications in nasal surgery. *J Craniofac Surg.* 2010;21:40–44.)

in culture medium at 37°C for 12–18 hours. The resulting tissue digestion solution was filtered and centrifuged to collect the chondrocytes and the cells were expanded *in vitro*.

To prepare the scaffold for the human ear shape, the ear of a 3-year-old child was cast using alginate as the impression material, and then a final cast of plaster was fashioned from the alginate impression. Using the plaster cast as a mold, PGA nonwoven mesh in about 100 μm thickness was coated with 1% (w/v) solution of polylactic acid (PLA) in methylene chloride. Following immersion, the fabric was removed and shaped into the form of a human ear using the plaster prosthetic mold.

To prepare a cell–scaffold construct, the ear-shaped scaffold was placed in a culture dish and seeded with 3 mL of chondrocyte suspension (1.5×10^8 cells) and placed in an incubator for 4 hours to allow seeded cells to attach on the scaffold and then culture medium (Hamm's F-12 supplemented with 10% fetal calf serum, 5 $\mu\text{g}/\text{mL}$ ascorbic acid, 292 $\mu\text{g}/\text{mL}$ L-glutamine, 100 U/mL penicillin, and 100 $\mu\text{g}/\text{mL}$ streptomycin) was added, and the construct was incubated *in vitro* at 37°C in 5% CO_2 for 1 week. As shown, the cell-seeded construct could maintain a good ear shape (Fig. 17.18A) and scanning electron microscope revealed good cell attachment on the scaffold and matrix production (Fig. 17.18B).

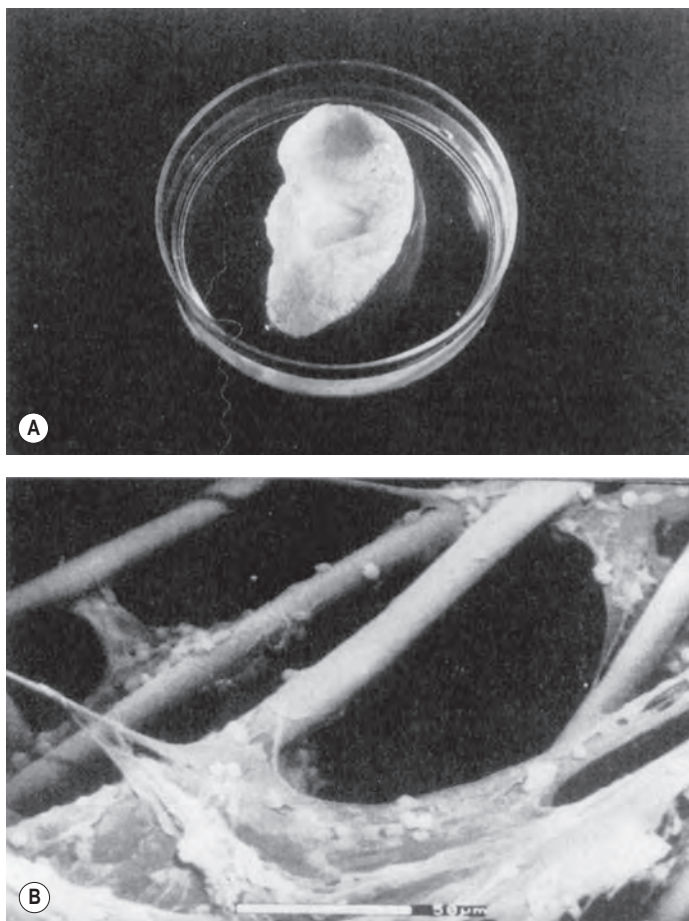


Fig. 17.18 Chondrocytes seeded on to the polymer ear mold *in vitro*. (A) Gross appearance of the ear polymer mold seeded with chondrocytes (1.5×10^6). (B) Scanning electron micrograph showing adherence of chondrocytes to polyglycolic acid device before implantation. (Reproduced from Cao Y, Vacanti JP, Paige KT, et al. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. *Plast Reconstr Surg.* 1997;100:297–302.)

After 1 week of *in vitro* culture, the cell-scaffold construct was implanted into the subcutaneous tissue of a nude mouse with the support of an external stent outside the skin to keep the shape (Fig. 17.19). As shown in Fig. 17.20, an ear cartilage structure is formed with the 3D shape that is almost identical to that of a human ear after 12 weeks of *in vivo* implantation. To verify the formation of engineered ear cartilage, tissues were harvested and subcutaneous tissues were stripped and the resulting gross view and histology confirmed a well-formed ear-shaped cartilage (Fig. 17.21). Through this pioneering study, the result provides an example of how to translate cartilage engineering research to plastic surgery application, particularly for engineered auricular reconstruction.⁶³

To explore the possibility of translating this technique to clinical application, a technique of *in vitro* engineering of human ear-shaped cartilage was developed with the assistance of computer-aided design (CAD) and computer-aided manufacture (CAM) technologies.⁶⁵

To proceed, computed tomography was employed to scan a patient's normal ear to collect the geometric data; the information was then processed by a CAD system to generate both positive and negative image data of the normal ear. The

resultant data were then input into a CAM system to print a mold with 3D structure of a normal ear in half size. Then, PGA unwoven fibers were inserted into the mold and coated with 0.3% PLA solution, thus generating a relatively solid ear-shaped scaffold material. The resulting scaffold was laser-scanned to generate a 3D image, which could be digitally compared with the original ear 3D image to analyze the similarity in 3D structure. As revealed in Fig. 17.22, the resulting ear-shaped scaffold achieved a similarity level of above 97% compared to the positive mold of original ear shape, indicating that the mold fabricated by CAD/CAM can fabricate a scaffold accurately into an ear shape that is mirror-symmetrical to the normal ear.

Afterwards, a total of 50×10^6 cells in 1 mL volume were evenly seeded on to the ear-shaped scaffold and cultured *in vitro* with medium change at regular time intervals. Interestingly, a human ear cartilage could be generated *in vitro* after 12 weeks of culture with good elasticity (Fig. 17.23). The engineered cartilage also revealed relatively mature histological structure of cartilage with lacuna structure formation and strong staining for Safranin-O and collagen II, as shown in Fig. 17.24. More importantly, the human ear-shaped cartilage formed *in vitro* could reach a morphological similarity of 82.6% to the positive ear mold, indicating that this technique not only can generate cartilage tissue *in vitro* but is also able

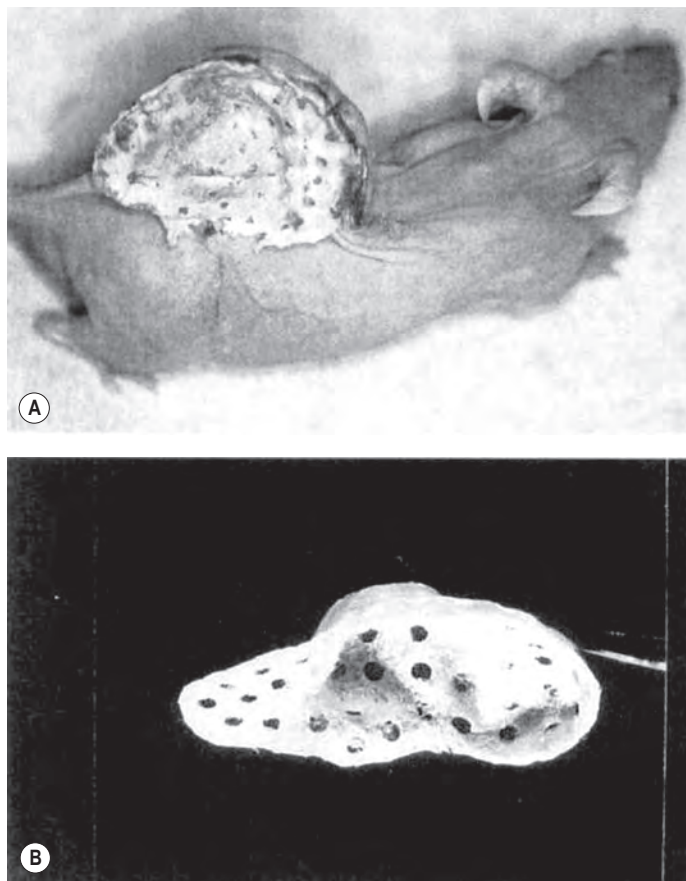


Fig. 17.19 An external stent was fixed on the outside skin of the polymer ear implant to maintain polymer mold shape (A) and the view of an external stent (B). (Reproduced from Cao Y, Vacanti JP, Paige KT, et al. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. *Plast Reconstr Surg.* 1997;100:297–302.)

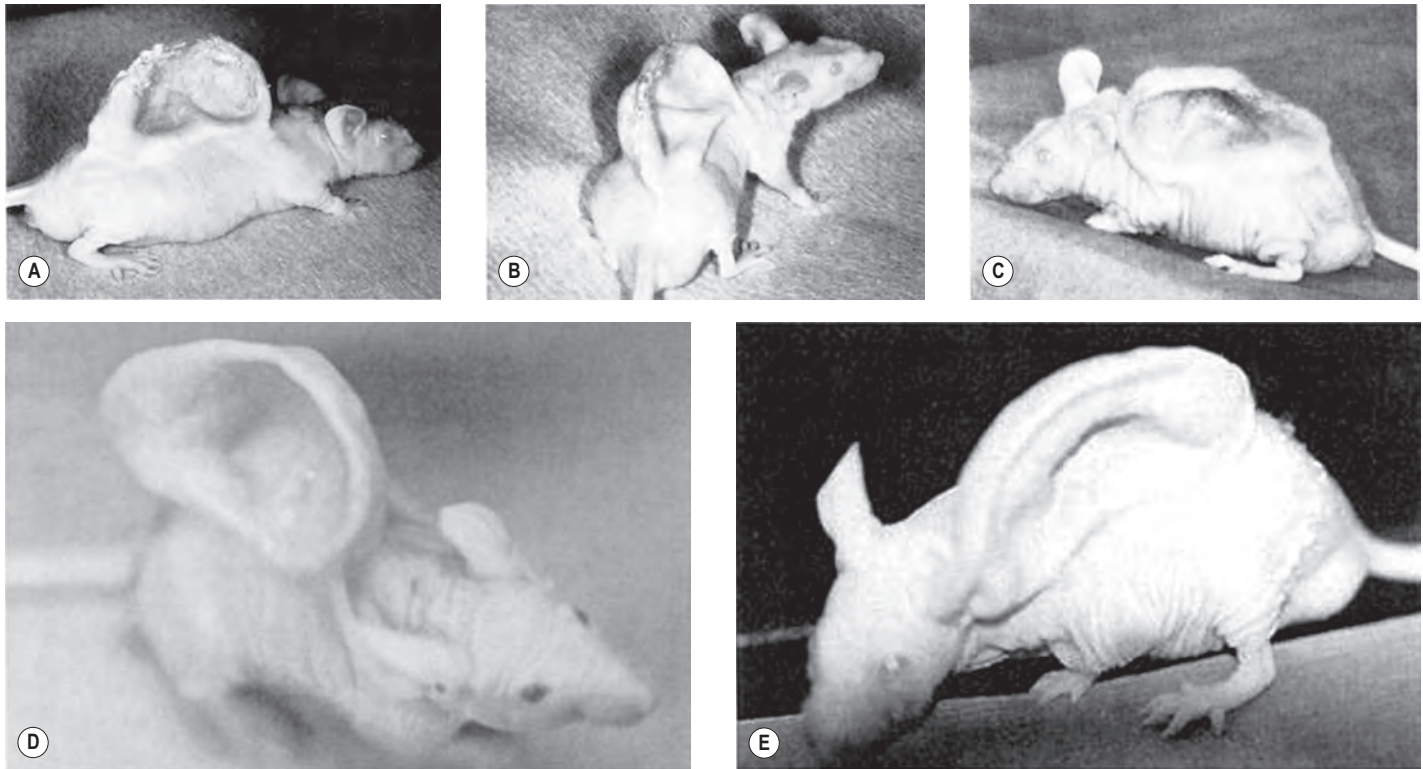


Fig. 17.20 (A–E) Gross appearance of the constructs 12 weeks after subcutaneous implantation into nude mice. Note the three-dimensional shape that is almost identical to that of a human ear. (Reproduced from Cao Y, Vacanti JP, Paige KT, et al. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. *Plast Reconstr Surg.* 1997;100:297–302.)

to maintain a designed 3D tissue structure (see Fig. 17.23).⁶⁵ Currently, continuous effort is being made in our center to study the fate of the *in vitro*-engineered ear-shaped cartilage after *in vivo* implantation and the progress in this area is expected to pave the way for the eventual clinical application of engineered human ear-shaped cartilage.

One of the unique properties of human ear cartilage is its excellent elasticity and flexibility that allow for torsion

and bending without causing a fracture. Mimicking such mechanical properties of the native tissue should also be an important consideration for engineering ear-shaped cartilage and its application. In 2005, Xu *et al.* reported a new method of generating flexible auricular cartilage.⁶⁶ In their study, auricular chondrocytes were isolated from swine ear cartilage by enzyme digestion and fibrin polymer was used as the scaffold. In addition, auricular perichondrium was

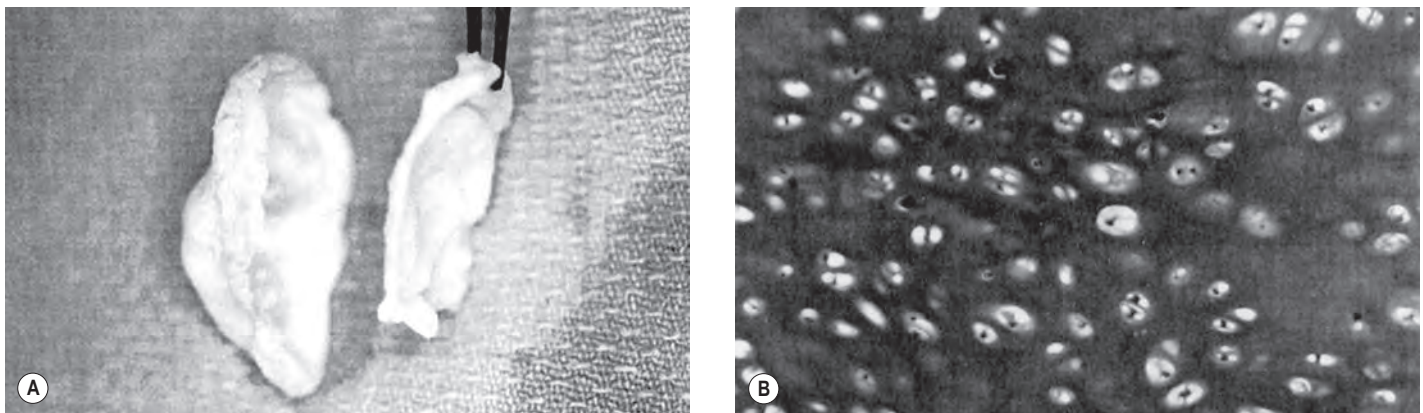


Fig. 17.21 (A) Gross view of engineered ear-shaped cartilage with (left) or without (right) external stent fixation. Note: fine contour of the new cartilaginous ear is maintained in the group with stent application. **(B)** Histology of engineered ear-shaped cartilage (hematoxylin and eosin, $\times 320$). (Modified from Cao Y, Vacanti JP, Paige KT, et al. Transplantation of chondrocytes utilizing a polymer-cell construct to produce tissue-engineered cartilage in the shape of a human ear. *Plast Reconstr Surg.* 1997;100:297–302.)

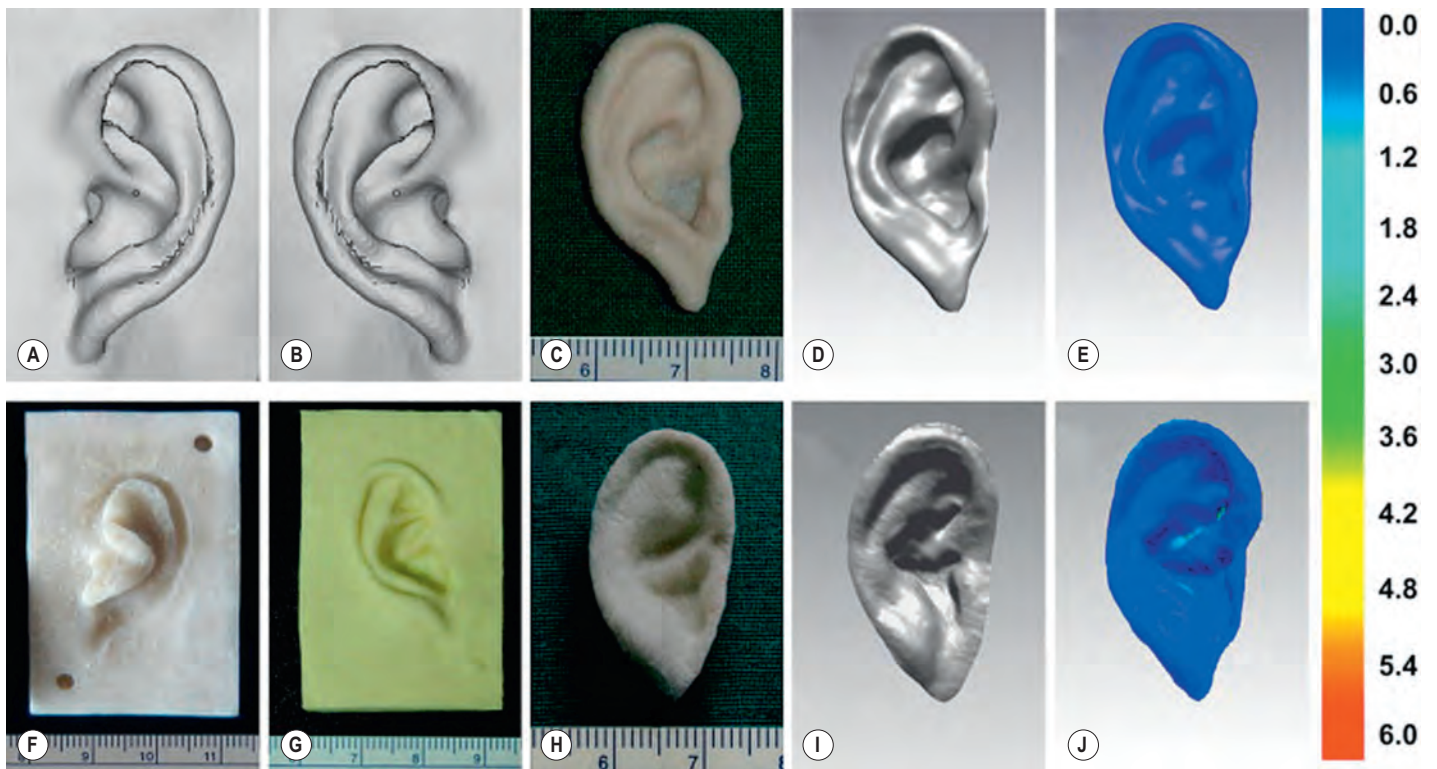


Fig. 17.22 Preparation and shape analysis of the ear-shaped scaffolds. (A) Three-dimensional (3D) image of the normal ear. (B) The mirror image of A. (C) The half-sized resin-positive mold. (D) Laser scan image of C. (E) Color map of D. (F) Inner part of the resin-negative mold fabricated by 3D printing. (G) Outer part of the negative mold cast from F with silicone rubber. (H) The ear-shaped poly(lactic acid)/poly(glycolic acid) scaffold. (I) Laser scan image of H. (J) Color map of I compared to E. Color bar at the right side represents similarity from highest (top, blue) to lowest (bottom, red). (Reproduced from Liu Y, Zhang L, Zhou G, et al. *In vitro engineering of human ear-shaped cartilage assisted with CAD/CAM technology*. *Biomaterials*. 2010;31:2176–2183.)

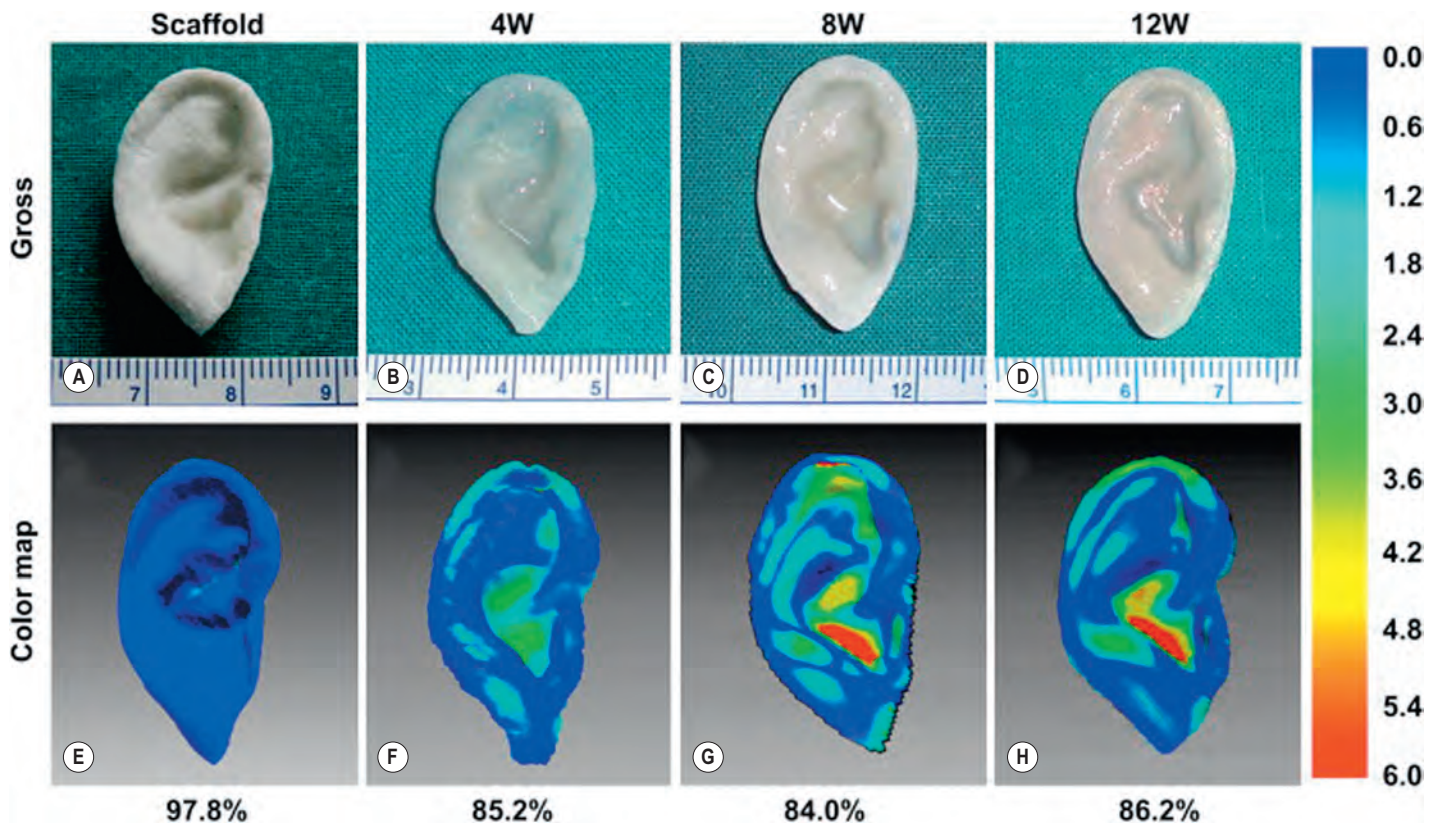


Fig. 17.23 Shape evaluation of the ear-shaped constructs. The scaffold shows an accurate ear-like structure (A) with a high similarity level compared to the positive mold (E). All the cell scaffold constructs largely maintain their original ear-like structures at 4 weeks (B), 8 weeks (C), and 12 weeks (D). Quantitative analysis shows over 84% shape similarity in all the samples (F–H) compared to the positive mold. (Reproduced from Liu Y, Zhang L, Zhou G, et al. *In vitro engineering of human ear-shaped cartilage assisted with CAD/CAM technology*. *Biomaterials*. 2010;31:2176–2183.)

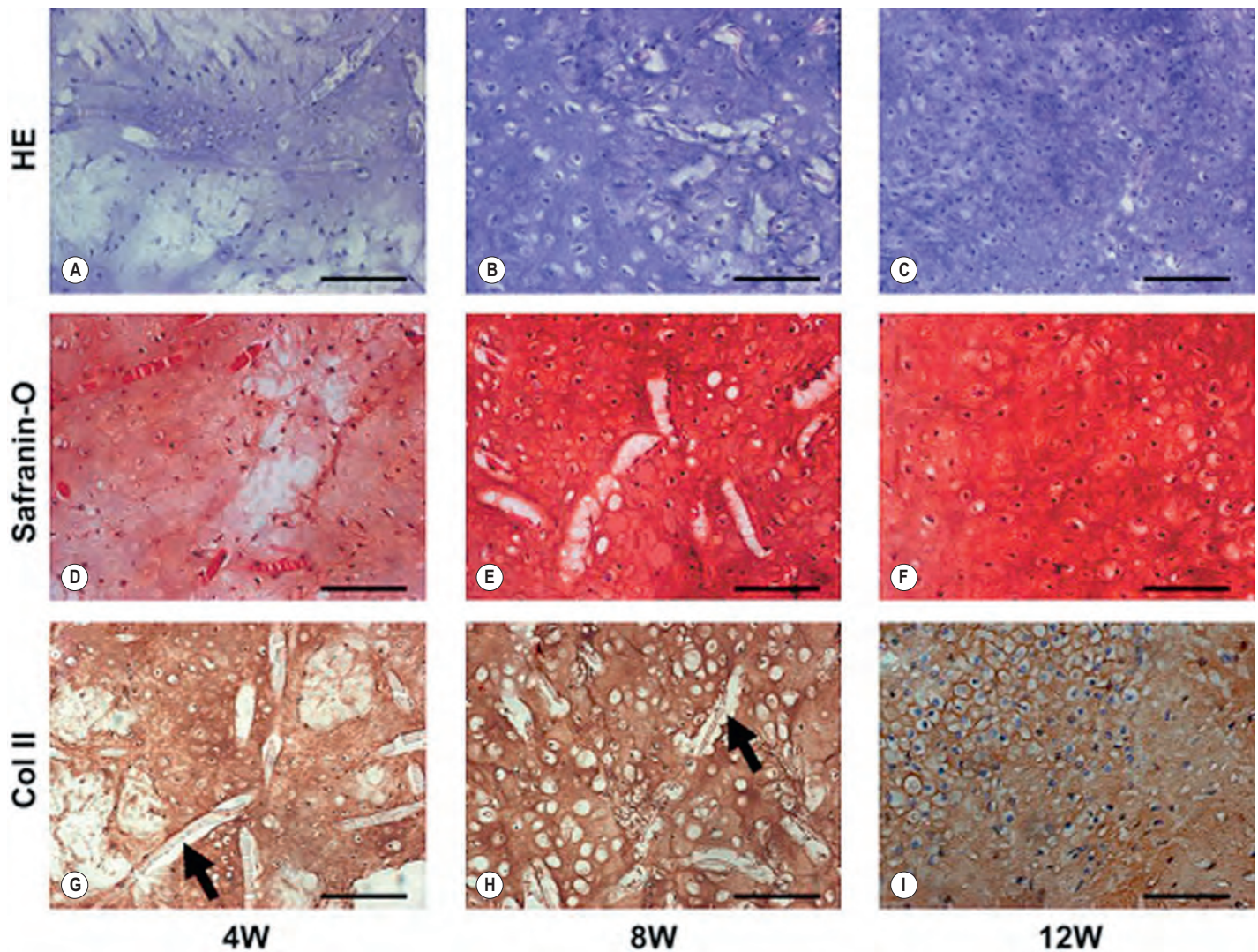


Fig. 17.24 Histological examinations of the *in vitro* ear-shaped constructs. At 4 weeks, the constructs form heterogeneous cartilage-like tissue along with undegraded polyglycolic acid fibers (**A, D, G**). With prolonged culture time, the histological structure of the constructs gradually becomes compact, accompanied by increased numbers of lacuna structures at 8 weeks (**B, E, H**). Homogeneous cartilage with abundant extracellular matrix and mature lacunae is observed at 12 weeks (**C, F, I**) with no visible scaffold residuals in the constructs. The black arrows indicate the undegraded polyglycolic acid fibers. Scale bar = 100 μ m. (Reproduced from Liu Y, Zhang L, Zhou G, et al. *In vitro* engineering of human ear-shaped cartilage assisted with CAD/CAM technology. *Biomaterials*. 2010;31:2176–2183.)

harvested and lyophilized. During the engineering process, equal volumes of both the chondrocyte fibrinogen suspension and the thrombin solution were mixed together to give rise to a chondrocyte–fibrin polymer suspension. The suspension was then placed into an ear-shaped well made from bone wax to allow for polymerization. To produce a flexible cartilage, the polymerized chondrocyte–fibrin construct was sandwiched between two layers of lyophilized swine perichondrium to form a trilayer, ear-shaped construct and then implanted into athymic mice subcutaneously. As a control, chondrocyte–fibrin construct without perichondrium was implanted as well. At 12 weeks of implantation, engineered cartilaginous tissue was formed in both the experimental and control groups.

Importantly, engineered cartilage laminated with perichondrium exhibited mechanical properties similar to those of the native swine ear, and could tolerate severe torsion and bending without fracture, although the 3D structure remains

to be improved. Histology also revealed good integration between the engineered cartilage and lyophilized perichondrium (**Fig. 17.25**). In contrast, the engineered cartilage of the control group became fractured after the test of torsion and bending. The result of this study indicates that lamination with lyophilized perichondrium is a reliable method of conferring elastic-like flexibility to an engineered ear cartilage. In the future, selection of a proper solid scaffold may help to control the precise and detailed structure better in order to generate flexible auricular cartilage with better 3D structure.⁶⁶

In addition to the experimental studies that employed animal chondrocytes, human chondrocytes have also been investigated for their ability to form engineered cartilage. Kamil *et al.* reported a comparative study of normal chondrocytes and microtia chondrocytes from patients and the results showed their similar abilities in cell proliferation and cartilage tissue formation, indicating that cartilage derived from

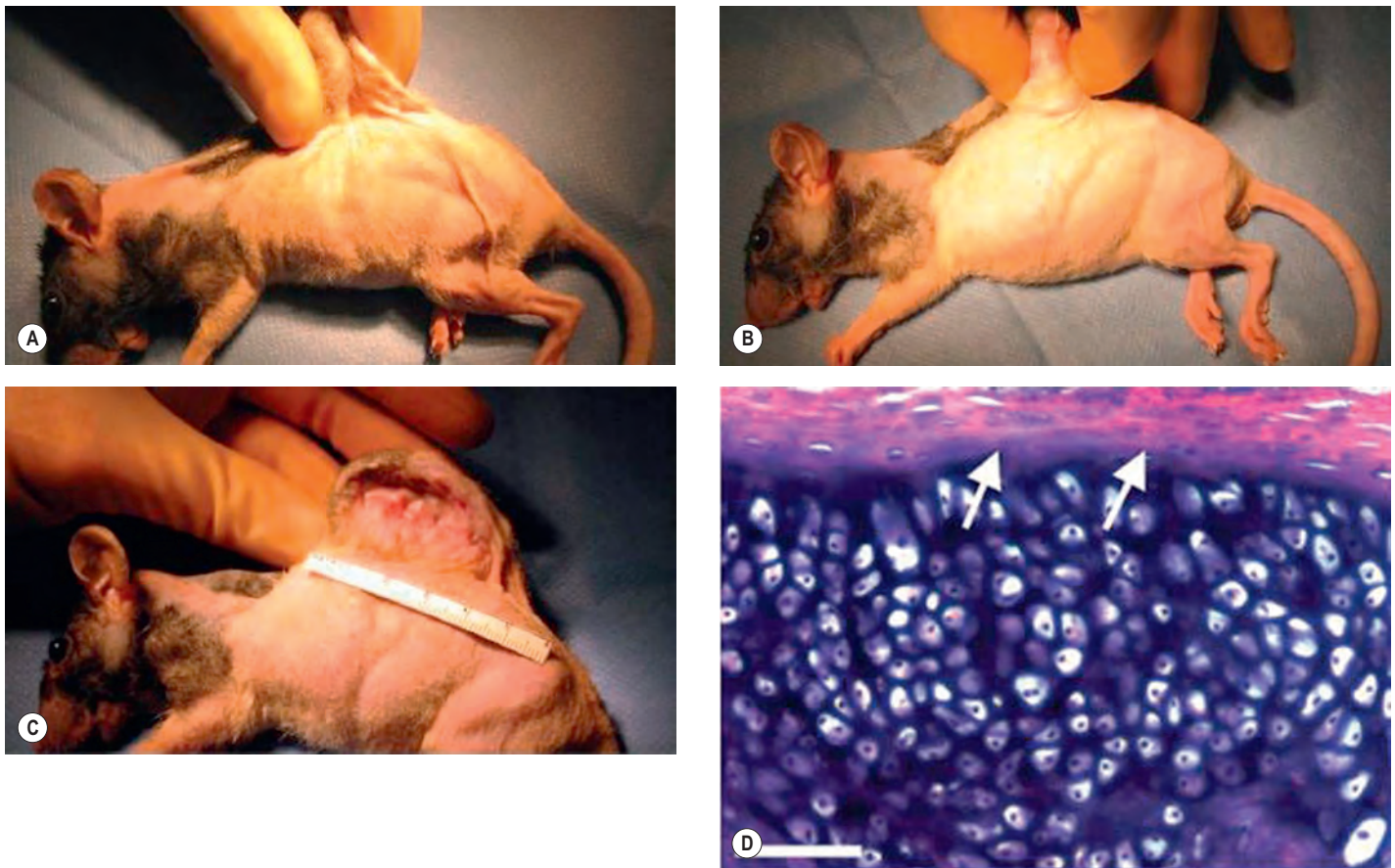


Fig. 17.25 (A, B) Gross mechanical testing of the ear-shaped framework at 12 weeks after insertion demonstrates a continued high degree of flexibility. (C) After mechanical testing, the framework easily recovers its initial shape. (D) Hematoxylin and eosin staining of flexible tissue-engineered cartilage (original magnification $\times 100$; bar = 100 μm), demonstrating the tight adherence at the interface between neocartilage and the lyophilized swine perichondrium laminate (arrows indicate interface). (Modified from Xu JW, Johnson TS, Motarjem PM, et al. *Tissue-engineered flexible ear-shaped cartilage*. *Plast Reconstr Surg*. 2005;115:1633–1641.)

microtia patients may potentially serve as the cell source to engineer human auricular cartilage.⁶⁷

Interestingly, Yanaga *et al.* reported a clinical trial of auricular reconstruction with fabricated human cartilage. In this trial, chondrocytes isolated from the cartilage remnant of microtia patients were cultured *in vitro* using a multilayer culture method, then the expanded cells along with their produced gelatinous chondroid matrices were collected into a syringe in the cell density of $0.5\text{--}1 \times 10^7$ cells per mL. Afterwards, 40–73 mL of cells/gelatinous matrices was injected into a subcutaneous pocket on the fascia of a patient's lower abdomen using a 16-gauge indwelling needle in order to generate an engineered cartilage block which could be sculptured into an auricular framework (Fig. 17.26). The results showed that a large piece of elastic cartilage was formed at the abdominal environment at 6 months postimplantation, which was also verified by histology examination. Importantly, this engineered cartilage block provides sufficient cartilage to create an ear framework. Furthermore, the framework could well support the reconstructed auricle without obvious absorption after being implanted for several years (see Fig. 17.26). This preliminary study provides important supporting evidence for the future clinical application of engineered auricular reconstruction.⁶⁸

Engineered cartilage for rhinoplasty and facial contouring

In addition to auricular reconstruction, rhinoplasty is another area where tissue-engineered cartilage may potentially be applied clinically. In contrast to auricular reconstruction, injectable cartilage is an important physical form for transplanting engineered cartilage.

In the early stage of tissue engineering research, injectable cartilage was employed to explore the feasibility of cartilage engineering using slowly polymerizing calcium alginate gels⁶⁹ or Pluronic gel,⁷⁰ amongst others. In recently published studies, human chondrocytes have also been confirmed to be able to form injectable cartilage using different injectable scaffolds.^{71,72}

Although most engineered injectable cartilage research remains at the experimental stage using either animal cells or an animal model, there are a few reports of the clinical application of injectable cartilage.^{73,74} Yanaga *et al.* reported a clinical trial of injecting cultured autologous chondrocytes for nasal augmentation. First, a piece of cartilage was harvested from auricular concha to extract chondrocytes and the cells were expanded *in vitro* into a gel-type cell-containing mass. Then, a subperiosteal skin pocket was created on the nasal dorsum

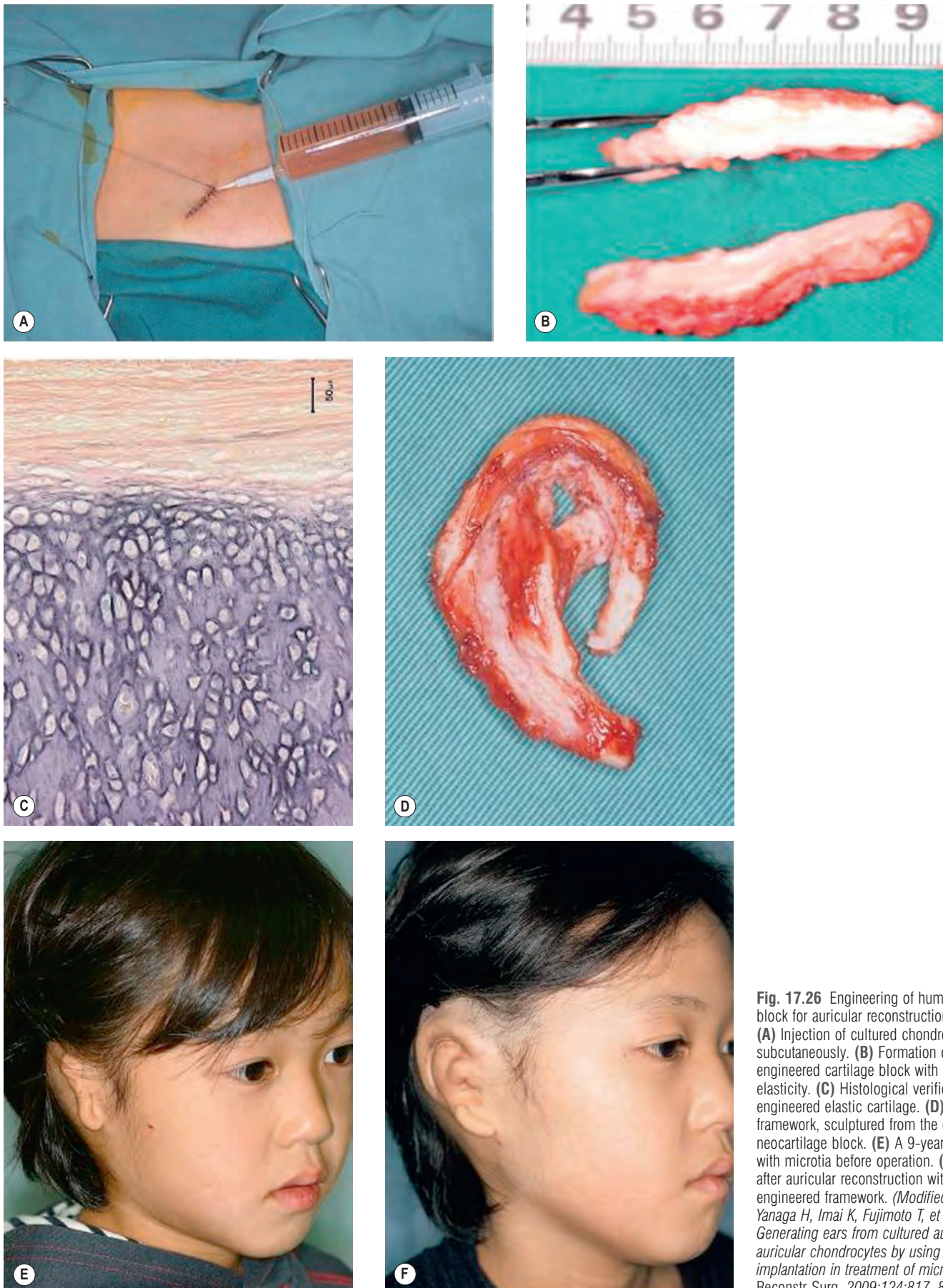


Fig. 17.26 Engineering of human cartilage block for auricular reconstruction.

(A) Injection of cultured chondrocytes subcutaneously. **(B)** Formation of engineered cartilage block with good elasticity. **(C)** Histological verification of engineered elastic cartilage. **(D)** An ear framework, sculptured from the engineered neocartilage block. **(E)** A 9-year-old boy with microtia before operation. **(F)** 2 years after auricular reconstruction with engineered framework. (Modified from Yanaga H, Imai K, Fujimoto T, et al. Generating ears from cultured autologous auricular chondrocytes by using two-stage implantation in treatment of microtia. *Plast Reconstr Surg.* 2009;124:817–825.)

of the patients and the chondrocytes were transplanted within a gel mass and the wound was closed. The implantation site was fixed with splint and tape for 3 weeks. Biopsy of injected tissue confirmed the formation of engineered cartilage after 1 month of implantation.

The procedure was applied in 8 patients for primary nasal augmentation or to correct a deformity resulting from silicone implant exposure or deviation. The patients were followed up for 6 months to 2 years and injected cartilage

could maintain its shape without resorption.⁷³ Later the same group further reported clinical trials in 32 patients for both nasal augmentation and facial contouring, with excellent clinical evaluation results and patient satisfaction in most cases.⁷⁴ Fig. 17.27 demonstrates the clinical outcome of injected cartilage for nasal augmentation. Additionally, the authors used injected autologous chondrocytes for chin augmentation and to correct temporal and forehead depressed deformity.^{73,74}

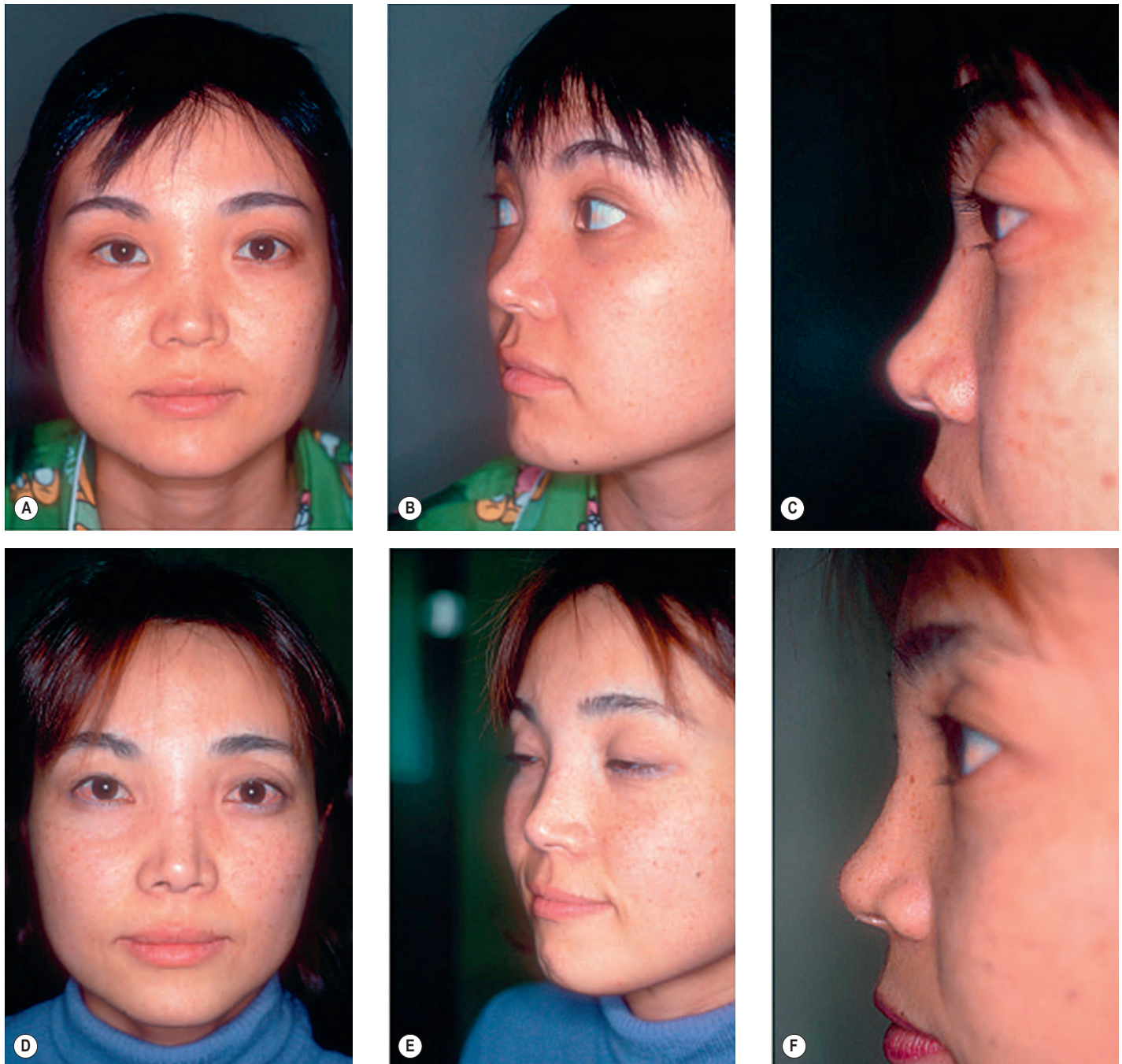


Fig. 17.27 A 35-year-old woman received injected cartilage to correct saddle-nose deformity. (A–C) Preoperative views. The autologous cultured auricular chondrocytes were grafted to the nasal dorsum. (D–F) Postoperative views after 34 months. The projection radix is higher than before grafting. The shape and contours of the nasal dorsum have aesthetically improved. Good contours have been maintained, and there has been no absorption of the grafted chondrocytes. (Reproduced from Yanaga H, Yanaga K, Imai K, et al. *Clinical application of cultured autologous human auricular chondrocytes with autologous serum for craniofacial or nasal augmentation and repair*. *Plast Reconstr Surg*. 2006;117:2019–2030.)

In addition to injectable cartilage, *in vivo*-engineered cartilage may potentially be used for nasal reconstruction. For example, Farhadi *et al.* reported the engineering of human nasal cartilage. In the study, chondrocytes were isolated from nasal septum and seeded onto nonwoven meshes of esterified hyaluronan (Hyaff-11). The cell-scaffold construct was cultured *in vitro* for 2 or 4 weeks and then implanted into nude mouse. The results showed that the cartilage was well formed after 2 weeks of *in vivo* implantation and the engineered cartilage exhibited good mechanical property.⁷⁵ Similar results were also reported in another study.⁷⁶ With enhanced mechanical strength, these *in vivo*-engineered cartilages may provide the autologous cartilage grafts potentially for septum or nasal alar reconstruction or nasal augmentation. *In vitro* engineering of cartilage with a nasal tip has been reported many years ago, aiming for nasal reconstruction with specifically shape-designed cartilage,⁷⁷ but its relatively weak mechanical strength might prohibit *in vitro*-engineered cartilage from immediate transplantation in nasal reconstruction.

Engineered cartilage for joint cartilage repair and reconstruction

Engineered cartilage may also serve as a composite graft to repair or reconstruct articular cartilage. There are two potential targets: temporomandibular joint (TMJ) and digital joints. In 2001, Weng *et al.* reported a preliminary study of mandible condylar reconstruction with tissue-engineered composites of bone and cartilage. In the study, scaffold of PLA-coated PGA was molded into the shape of human mandible condyle and respectively seeded with osteoblasts and chondrocytes followed by *in vivo* implantation in nude mouse. After 12 weeks, a condyle-shaped bone tissue was well formed with articular cartilage on the surface and histology confirmed the formation of trabecular bone and hyaline cartilage, suggesting a potential approach for clinical TMJ reconstruction.⁷⁸ In addition, engineered cartilage was proposed for TMJ disc reconstruction to potentially restore TMJ function.⁷⁹

Cartilage presents as the major tissue component in interphalangeal joints or metacarpophalangeal joints and plays an important functional role. As early as 1999, Isogai *et al.* reported a preliminary study on constructing small phalanges and the whole joints using a tissue-engineering approach.⁸⁰ The approach included the use of PLA or PGA as the scaffold and fresh bovine periosteum was harvested to wrap around the scaffold for bone engineering. Additionally, chondrocytes and tenocytes were seeded on the scaffold to form articular cartilage and associated tendon tissue. The results showed that a preliminary composite tissue formed with the shape and dimensions of human phalanges as well as the joints.⁸⁰ A study with much larger sample size was also performed to engineer composite tissue of human phalanges and a small joint, with successful results.⁸¹ Although these studies were preliminary, the results revealed the promise of the future application of engineered cartilage in joint reconstruction.

Future directions

Despite a few preliminary clinical trials of engineered cartilages in auricular and nasal reconstruction, there remains much to do in both basic and applied research prior to true

translation of cartilage research to clinical application. To fulfill the goal, the following areas may represent future directions.

Stem cell-based cartilage engineering

Although both auricular and nasal cartilages have been used as the sources to extract chondrocytes, the available tissue amounts are limited. Although more tissue volume can be harvested from rib cartilage, the amount of cells that can be harvested is limited due to low cellular density. Stem cells, particularly adult stem cells, have become an alternative cell source because of their multidifferentiation potential (including chondrogenic) and strong proliferation capability.

The adult mesenchymal stem cells derived from bone marrow and adipose tissue are the most feasible cell source for cartilage engineering.⁸² Chondrogenic differentiation can be achieved with growth factor induction⁸³ or co-culture with chondrocytes⁸⁴ or with chondrogenic matrices.⁸⁵ In recent years, mimicking native histoarchitecture and the molecular signaling of cartilage microenvironment in scaffold design have been considered important to facilitate stem cell chondrogenic differentiation and cartilage formation.⁸⁶ Therefore, optimization of chondrogenic induction regime by proper combination of paracrine factors, chondrogenic matrices, and suitable topographical structure of scaffold is likely to enhance chondrogenic differentiation of stem cells, and improve the structure and function of stem cell-engineered cartilage.

In vitro engineering of cartilage with enhanced mechanical strength

As described above, the application of plastic surgery requires immediately available cartilage graft to generate an auricular or a nasal frame for reconstructive surgical procedures. *In vivo* engineering cartilage, first using the human body as a bioreactor and then reshaping the *in vivo*-engineered cartilage block into a desired frame, would require at least two-stage operations.⁶⁸ Furthermore, patients may undergo unnecessary suffering if the first stage of *in vivo* engineering fails. Therefore, *in vitro* cartilage engineering can not only avoid two-stage operations, but also reduce the risk of failure because more back-up engineered cartilages can be made simultaneously *in vitro* without causing patient suffering.

Today, *in vitro* cartilage engineering has already been proven feasible by experimental studies using either chondrocytes⁶⁵ or mesenchymal stem cells.⁸⁷ Nevertheless, the mechanical strength of *in vitro*-engineered cartilage remains relatively weak compared to that of *in vivo*-engineered cartilage.⁸⁸ This is likely caused by the differences between *in vitro* and *in vivo* microenvironments, and the latter can promote the maturation of engineered cartilage and thus lead to differential expression of key matrix molecules such as collagen IX and pyridinoline, and enhanced mechanical strength.⁸⁸ Although it remains difficult to define the environmental mechanism, partially mimicking *in vivo* microenvironmental factors may help to enhance the mechanical property of *in vitro*-engineered cartilage. For example, when an articular cartilage was engineered in a bioreactor with dynamic loading, it was found that continuous dynamic loading could significantly increase Young's modulus of the engineered cartilage. In addition, the loaded cartilage increased the production of cartilage oligomeric matrix protein and collagens II and IX.⁸⁹ In the

future, mechanical loading as well as other factors that are able to facilitate collagen maturation may represent one of the future directions for *in vitro* cartilage engineering.

Design and precise control of engineered cartilage 3D structure

For engineered cartilage application in auricular and nasal reconstruction, precise control of 3D structure is necessary to

achieve the goal. As previously described, a CAD/CAM system is essential to collect the 3D information and to fabricate the scaffold with a specific 3D structure that matches a patient's own auricular or nasal structure. In addition, the fabrication of a suitable scaffold that is able to maintain the precise 3D structure during cartilage formation may be an important consideration. Furthermore, an inner core stent with slow degradation rate may help to maintain the 3D structure if the inner core starts to degrade after mature cartilage formation.



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Repair and grafting of bone

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SYNOPSIS

- This chapter will concentrate on the principles and concepts of bone repair, grafting, and reconstruction.
- The embryology, physiology, microanatomy, and histochemistry of bone will be reviewed.
- Principles of mechanotransduction and cellular mechanisms of bone turnover will also be discussed.
- Pathophysiology of traumatic injury to bone (fractures, segmental loss, defects) will be categorized and reviewed.
- Bone-remodeling mechanisms (osteoconduction, osteoinduction, osseointegration) will be described.
- After a brief history of autogenous bone grafting, the clinical application of bone transfer and transplantation will be captured by a brief atlas of harvest of each subtype.
- The reader will also be provided with a brief overview of bone substitutes.

Microanatomy and histochemistry

Bone is a complex structure that serves many roles within the body. It is crucial for maintaining mineral homeostasis, provides protection to internal organs, and offers structural support for locomotion and stature. Osseous tissue undergoes continuous remodeling, during which old bone is degraded and replaced by new bone. Most organs in the adult human undergo repair with scar tissue after injury. Bone, however, regenerates, making it a unique organ system.

The formation of bone occurs by either intramembranous ossification or endochondral ossification. Direct condensations of mesenchymal stem cells (MSCs) initiate the process of intramembranous ossification to create flat bones of the craniofacial skeleton. During intramembranous ossification, osteoblasts lining skeletal surfaces deposit new bone upon previously laid bone in a process called *apposition*.

Alternatively, endochondral ossification is characterized by the formation of an MSC-derived hyaline cartilage template that is subsequently replaced by bone. Endochondral ossification is responsible for the development of tubular long bones of the appendicular skeleton as well as the bones of the vertebral column and pelvis.¹⁻⁴

Bony tissue contains osteocytes located within open cavities called *lacunae*. Osteocytes project radiating processes through microscopic canaliculi that adjoin neighboring lacunae. Osteocytic cytoplasmic processes are linked to one another via gap junctions,⁵ through which osteocytes communicate.⁶

Cortical versus cancellous bone

The skeleton is comprised of cortical and cancellous bone (Fig. 18.1). Cortical bone is compact and forms the outer skeleton. It accounts for 80% of osseous tissue. Cortical bone is dense and strong to support the body and protect organs. A bilayered cellular membrane (*periosteum*) covers cortical bone. The outer layer is composed of a dense fibrous membrane containing flat fibroblast-like cells and serves as an attachment for muscles and tendons. Large plump cells line the inner periosteal layer (*cambium layer*) and can differentiate into osteoblasts upon stimulation. Bone also contains a thin layer of vascular connective tissue (*endosteum*) that lines the medullary cavity.

The primary functional unit of cortical bone is the osteon or haversian system (Fig. 18.2). An osteon contains concentric layers of cortical tissue (lamellae) that surround a central haversian canal that contains vascular and nervous tissue. Nutrient vessels within haversian canals anastomose to blood vessels in bone marrow and periosteum via the perpendicular running Volkmann's canals.

Cancellous or trabecular bone comprises approximately 20% of the skeleton. Relative to cortical bone, cancellous bone is porous and is located deep within the medullary cavity, typically at the ends of long bones. It consists of bony trabeculae oriented along the lines of stress. Cancellous and cortical bone are chemically equivalent; however, cancellous bone has increased metabolic activity due to its greater surface area for

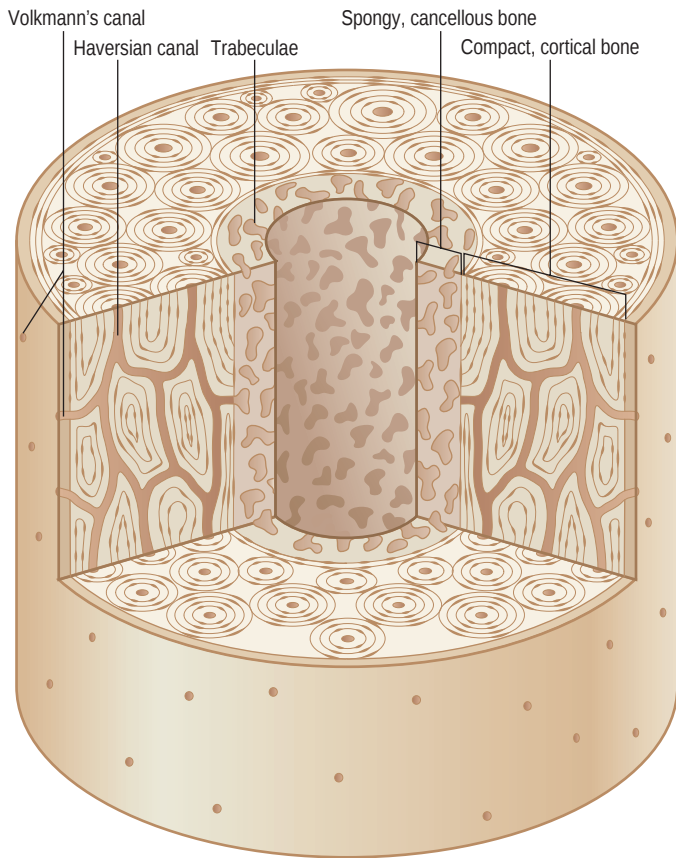


Fig. 18.1 Diagrammatic representation of axial compact cortical bone microarchitecture.

remodeling. Cancellous bone provides internal support for bone marrow elements and cortical bone.

The chemical composition of bone

Inorganic phase

Bone is a calcified tissue composed of 60% inorganic matter, 30% organic matter, and 10% water. The inorganic component of bone makes up approximately 40% of bony volume, while the organic component and water comprise 35% and 25%, respectively.^{7–10} The inorganic phase primarily consists of the mineral crystal hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$), which measures 20–25 nm in length, 15 nm in width, and 2–5 nm in thickness.⁷ It is the hydroxyl endmember of the apatite group; however, impurities arise when the hydroxyl group is replaced by potassium, magnesium, or sodium; or when carbonate replaces the phosphate group.^{7,10–14} By storing them as a mixture within impure hydroxyapatite, bone provides a reservoir of various minerals within the body.

Organic phase

The organic component of bone (demineralized organic bone matrix or osteoid) is deposited by osteoblasts during bone formation. Osteoid is primarily composed of type I collagen, but also includes many noncollagenous proteins.⁹ Collagen is a trilaminar protein consisting of two $\alpha 1$ chains and one $\alpha 2$ chain that form a distinct right-handed helical structure. Within the rough endoplasmic reticulum of osteoblasts, procollagen undergoes hydroxylation and glycosylation before

transfer to the Golgi apparatus, where it is packaged and secreted. Extracellularly, procollagen peptides are cleaved into tropocollagen. The copper-dependent enzyme lysyl oxidase mediates covalent cross-linking within and between tropocollagen molecules to create mature collagen fibers. The strength of bone is derived from interactions between collagen fibers and inorganic minerals.

The cellular composition of bone

Three cell types are predominantly found in bone: osteoblasts, osteocytes, and osteoclasts (Table 18.1).

Osteoblasts

Histology and function

Osteoblasts are derived from MSCs that have the capacity to differentiate into several connective tissue cell types.¹⁵ Within the appropriate osteogenic environment, MSCs differentiate into osteoprogenitor cells, thereby committing to an osteoblastic lineage. Osteoprogenitor cells are ubiquitous in bone, located within Volkman's and haversian canals, the cambium layer of periosteum, endosteum, and within perivascular tissue adjacent to bone.¹⁶

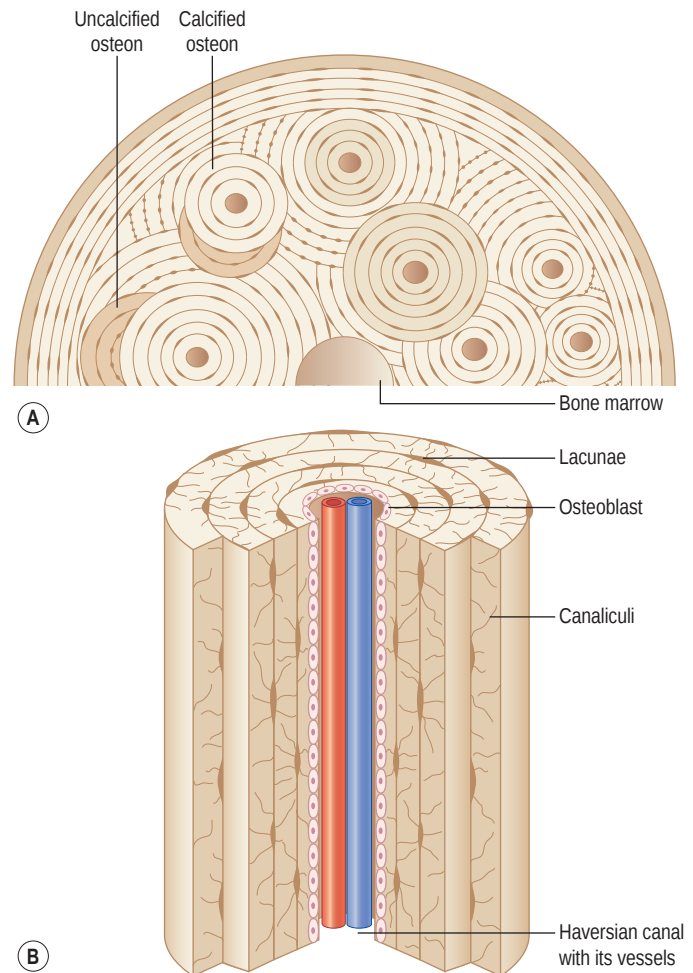


Fig. 18.2 (A) Cross-section of compact bone as seen by microradiography. Note that the osteons are oriented in the longitudinal axis of long bone. The dark masses represent recent decalcified osteons. The light masses represent older calcified osteons. (B) A single osteon of the haversian system.

Table 18.1 Bone cells

Cell type	Morphology	Location	Function	Source	Precursor cell	Differentiation product
Osteoblast	Rounded, basophilic cells Stain strongly for alkaline phosphatase	External surfaces of bone in areas of active remodeling and bone formation Bone surfaces in fractures	Produce bone matrix	Periosteum Endosteum Bone marrow ? Others	Preosteoblast ? Bone-lining cells	Osteocyte
Osteocyte	Stellate cells with thin cytoplasmic processes	Embedded in lacunae	Exact function unknown Potential functions: Mechanosensory Mineral homeostasis Bone resorption	Osteoblasts that become embedded in osteoid	Osteoblasts	Terminally differentiated cell
Osteoclast	Large, multinuclear cells with ruffled border Stain positive for tartrate-resistant acid phosphatase	Endosteal and periosteal surfaces of bone in areas of active remodeling On fractured bone surfaces	Bone resorption	Bone marrow Spleen ? Lung, peritoneum, peripheral blood	Hematopoietic stem cell	None

Osteoblasts are plump, basophilic cells located on the external surfaces of bone at areas of active bone formation during development and fracture repair. They have a vast endoplasmic reticulum for robust collagen production and contain many mitochondria and a large Golgi apparatus to package and secrete procollagen. Osteoblasts are responsible for the production of bony matrix and facilitate the mineralization of osteoid.^{16–18} Some osteoblasts will eventually become surrounded with bony matrix and terminally differentiate into osteocytes.

During osteoprogenitor cell differentiation, cells halt proliferation and start expressing proteins characteristic of an osteoblastic lineage. Preosteoblasts secrete proteins (e.g., alkaline phosphatase (ALP)) that denote early osteogenesis,^{4,19,20} and also begin to produce bony matrix proteins. As the differentiation process ensues, cells display a basophilic appearance, stain strongly for ALP, and lose the ability to proliferate. Mature osteoblasts deposit significant osteoid. They also play a role in many other processes as indicated by their secretion of numerous cytokines and noncollagenous proteins that have pleiotropic effects, as well as factors important for myelopoiesis.^{16,21} Differentiated osteoblasts affect bone metabolism and mineral homeostasis by interacting via surface receptors with parathyroid hormone and 1,25-dihydroxyvitamin D. Most osteoblasts ultimately undergo apoptosis or become bone-lining cells. However, 20% differentiate into osteocytes.²²

Regulation of osteoblast differentiation

Major signaling pathways

Under the control of multiple signaling pathways, preosteoblasts differentiate into mature osteoblasts. The Wnt pathway,^{23–26} the TGF- β /BMP superfamily,^{19,27–29} notch signaling,^{30–32} hedgehog proteins,^{33–36} and fibroblast growth factors^{37–40} (FGFs) have all been implicated in the molecular

signaling of osteogenesis. Although the exact mechanisms of osteogenesis are complex and only partially elucidated, advances have been made regarding the initiation and molecular control of this process. Wnt/ β -catenin signaling has been shown to control the differentiation of both osteoblasts and osteoclasts, which may be important in postnatal bone acquisition.⁴¹ Wnt/ β -catenin signaling is also important during skeletogenesis in the fetus, and is considered to be partially responsible for both osteoblast and chondrocyte differentiation.^{42,43} Notch signaling is a highly conserved signaling system involving cell–cell communication. In addition to cell fate division and homeostatic maintenance, the notch pathway is believed to be important in osteogenesis because of notch1–BMP-2 interactions that promote osteogenic differentiation.⁴⁴ Additionally, Engin *et al.*⁴⁵ showed with osteoblast-specific gain of Notch function studies that Notch not only stimulates terminal osteoblast differentiation, but that it also plays a role in the proliferation of immature osteoblasts. In addition, loss of notch signaling is associated with the expression of an osteoporotic phenotype.⁴⁵

Hedgehog signaling plays a role in many embryonic processes and also is involved with the maintenance of stem cells in adults. There are three mammalian Hedgehog orthologs: Desert, Sonic, and Indian. Sonic Hedgehog and Indian Hedgehog both have important roles in osteogenesis.^{33,34,46–49} Specifically, Indian Hedgehog is critical for endochondral bone formation,⁵⁰ whereas Sonic Hedgehog appears to be important for skeletal patterning.⁵¹

Transcriptional regulation

Many transcription factors play a significant role in osteogenesis. Runt-related transcription factor 2/core-binding factor alpha 1 (RUNX2/CBF α -1) and Osterix have important effects on osteoblast differentiation.^{52–57} RUNX2 is the mammalian homolog of the *Drosophila* transcription factor Runt and is

believed to be evolutionarily conserved in humans to serve a critical role throughout the many steps of osteoblastogenesis, including osteoblast induction, proliferation, and maturation. Homozygous deletions of the Runx2 gene are uniformly lethal in mice due to a complete lack of mineralized bone matrix.⁵³ Runx2 haploinsufficiency causes cleidocranial dysplasia, an autosomal-dominant disease in humans characterized by hypoplastic clavicles, dental deformities, shortened stature, brachycephaly, hypertelorism, and other skeletal defects.⁵⁸ While the exact mechanisms that control the regulation of Runx2 have not been fully decoded, studies have shown that various histone acetyltransferases are important Runx2 cofactors.^{59,60} Additionally, microRNAs appear to regulate Runx2 protein expression.⁶¹ MicroRNAs play critical roles in stem cell function,^{62,63} and thus may have important clinical implications for diseases due to dysfunctional MSC/Runx2 interactions. Many other regulators also play an important role in Runx2 function^{64–70}; however, their exact roles are currently under study.

The zinc finger-containing protein osterix (Osx) is also a key transcription factor to bone formation.^{55,71} Osx-null mice form neither cortical nor cancellous bone. Unlike Runx2-null mice, however, Osx-null mice still produce normal cartilage.⁷² As a result of the findings that Osx expression is absent in Runx2 knockout mice, whereas Runx2 expression is normal in Osx-null mice, the Osx gene is thought to be downstream to Runx2.⁵⁵ Nishio *et al.*⁷³ confirmed this using overexpression experiments to show that Runx2 transactivates the Osx gene promoter significantly, indicating that there is a Runx2-binding element within the promoter region.

The signaling pathways and transcription factors responsible for osteoblastogenesis are exquisitely detailed elsewhere.^{74,75}

Osteocytes

Histology

Osteocytes are terminally differentiated cells of the osteoblast lineage and comprise 90–95% of all bone cells. Despite being the most abundant cell in bone, osteocytes are the least well characterized. Osteocytes are located within lacunae. Multiple cytoplasmic processes radiate from osteocyte somas and travel through canaliculi between lacunae. Gap junction connections between adjacent cytoplasmic processes enable osteocytes to communicate with one another. Osteocytes communicate with osteoblasts by way of this canalicular network as well. Processes also extend to the haversian canals so that osteocytes can rid themselves of waste products and receive nutrients necessary for survival. Relative to osteoblasts, osteocytes have qualitatively similar organelles, but the organelles are smaller in both size and number.⁷⁶

Osteocyte function

Bone is a dynamic substance that maintains its viability by constantly adapting to the environment in which it lives. Victim to mechanical loading and various traumas, bone must have a way to recognize such stressors. It is believed that osteocytes are mechanosensory cells that translate (via mechanotransduction) physical stress into chemical and/or electrical signals that stimulate bone remodeling.^{77–79} This hypothesis has been derived from various lines of evidence. Anatomically, osteocytes form a syncytium with surrounding cells via their cellular processes. These connections may provide

communication between mechanical stimuli and effector cells (osteoblasts and osteoclasts). Recent evidence has shown that osteocyte processes also attach to ECM proteins and may mediate mechanotransduction by the amplification of shear stress experienced at the ECM.⁸⁰ In addition, mechanical loading alters osteocyte gene expression. Osteocytes rapidly produce increased levels of *c-fos*, IGF-1, prostaglandin (PG), and nitrous oxide (NO) when mechanically stimulated.^{81–83} These and many other molecules (see below) have numerous effects on bone turnover. Molecular studies have implicated the activation of the Wnt/ β -catenin pathway in response to loading.^{84,85} The osteocytic Wnt/ β -catenin pathway appears to be triggered by crosstalk with various signaling pathways when the osteocyte senses a load strain, thereby decreasing negative regulators of the Wnt/ β -catenin pathway,⁸² an important regulator of bone mass. Finally, Tatsumi *et al.*⁸⁶ have shown that targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction.

One potential function of the osteocyte, termed periosteocytic osteolysis, has remained elusive. Osteocytes may fulfill an osteoclast-like activity by resorbing varying amounts of calcified bone matrix surrounding their lacunae. Evidence for this comes from studies that have shown a larger than expected size of lacunae in conditions characterized by increased bone resorption.^{87–89} Additionally, the administration of parathyroid and thyroid hormone has been shown to induce microradiographic enlargement of lacunae, thought to be the result of the hormones' actions on osteocytes.^{90,91} Recently, Wysolmerski⁹² suggested that osteocytes have a role in coordinating bone and mineral metabolism during reproductive cycles. Specifically, osteocytes reversibly remodel perilacunar and pericanalicular bone during lactation by removing mineralized tissue in order to liberate calcium (and potentially phosphorous) for milk production. This tissue is then replaced during the recovery period after weaning.

Osteoclasts

Histology and function

Osteoclasts are multinucleated cells primarily responsible for bone resorption, a process necessary for bone growth, tooth eruption, fracture repair, and calcium homeostasis. Osteoclasts typically have between three and 25 nuclei per cell and are approximately 40 μ m in diameter. Histologically, osteoclast cytoplasm has a characteristic homogeneous, “foamy” appearance due to a high concentration of vesicles and vacuoles. Osteoclasts are derived from hematopoietic progenitor cells and are related to the monocyte/macrophage lineage. Osteoclasts are found on the endosteal and periosteal surfaces of bone in areas of active remodeling.

Bone resorption is a complex process by which crystalline hydroxyapatite is dissolved and organic bone matrix is degraded. *In vitro* bone resorption models using primary osteoclast isolates provided the basis for the resorption cycle.^{93,94} The cycle is a complex series of actions which includes osteoclast migration to the resorption site and attachment to bone, membrane polarization, dissolution of hydroxyapatite followed by degradation of organic bone matrix, removal of degradation products, and osteoclast inactivation or apoptosis.⁹⁵ Clinically, bone resorption is an extremely important process, as evidenced by pathologic conditions characterized by dysfunctional resorption. For example, increased osteoclastic function

leads to excess bone resorption, thereby causing osteoporosis. In contrast, osteoclast underactivity decreases bone resorption, which causes osteopetrosis.

Bone resorption is key for both bone remodeling at sites of injury and also as a mechanism of calcium homeostasis. Osteoclasts are stimulated to resorb bone by growth factors and cytokines secreted by local osteoblasts.⁹⁶ Once osteoclasts localize to the area in need of resorption they form a tight seal that separates the area of bone to be resorbed from the extracellular environment. Evidence has pointed to integrins (in particular integrin $\alpha_v\beta_3$) and cadherins as playing a prominent role in the attachment of this sealing zone.^{97–99} Myosin and actin-binding proteins are also important for such attachments.^{100,101} After sealing zone attachments are completed, osteocytes polarize such that the area adjacent to the resorbing bone surface becomes ruffled. The ruffled border is a specialized membrane domain formed by the fusion of intracellular acidic vesicles and functions as the osteocyte's resorbing organelle.^{102,103} Finger-like projections from the ruffled border increase the effective surface area of resorption. Before proteolytic cleavage of the organic matrix occurs, osteoclasts dissolve hydroxyapatite crystals by targeted secretion of hydrochloric acid through the ruffled border toward the resorption pit (Howship's lacuna).⁹⁵ After the dissolution of inorganic matter, many proteolytic enzymes, including matrix metalloproteinase-9 and cathepsin K, are secreted into the resorption lacuna to degrade the organic components of bones.^{104,105} Both phases of bone are subsequently removed from the resorption lacuna via transcytosis through the ruffled border and sent to the secretory domain of the osteoclast, which then expels these degradation products into the extracellular space outside the osteoclast.^{106–108} The osteocytic marker tartrate-resistant acid protease (TRAP) has been localized to transcytotic vesicles of resorbing osteoclasts, and is believed to generate reactive oxygen species that degrade matrix degradation products within these vesicles.¹⁰⁹

Osteoclast differentiation

The mechanisms surrounding osteoclast differentiation are complex and have been the subject of intense study. Depending on local stimuli, hematopoietic stem cells may differentiate into osteoclasts, macrophages, or dendritic cells. Macrophage colony-stimulating factor (M-CSF) and receptor activator for nuclear factor κ B (RANK) and RANK ligand (RANKL) are early mediators that signal osteoclastogenesis.^{110–115} In murine studies, M-CSF is functionally lacking in *op/op* mice, which express an osteopetrotic phenotype.^{116,117} In addition, in order for osteoclastogenesis to commence, RANKL (found on the cellular membrane of osteoblasts) must interact with RANK, a receptor found on osteoclast precursors.^{118–120} RANK–RANKL interaction must occur in order for osteoclast precursor cells to begin expressing phenotypic markers (e.g., TRAP) that characterize osteoclasts. Similar to *op/op* mice with functionally absent M-CSF, RANK and RANKL knockout mice also express an osteopetrotic phenotype.^{113,115,121}

Osteoprotegerin (OPG), a TNF-related soluble protein secreted by osteoblasts, is also an important regulator of osteoclastogenesis. OPG has effects on bone density and bone mass^{118,122} by acting as a decoy receptor for RANK, thereby blocking RANK–RANKL interaction. Transgenic mice that overexpress OPG suffer from an osteopetrotic

phenotype¹²², while OPG knockout mice display an osteopetrotic phenotype.^{123,124}

The RANK molecule lacks enzymatic activity, and thus must recruit adaptor proteins when stimulated by RANKL to promote differentiation.^{125–127} TNF receptor-associated factor (TRAF) family members appear to be important adaptor proteins, with TRAF6 serving the most critical role.^{128–130} TRAF6 knockout mice develop severe osteopetrosis as a result of either the dysfunction or total absence of osteoclasts.^{131,132} Moreover, TRAF6 activates NF- κ B, another essential modulator of osteoclast differentiation.^{133,134} NF- κ B enters the nucleus of osteoclasts stimulated with RANKL, and regulates transcription of target genes critical for osteoclastogenesis.¹³⁵

Extracellular matrix

The extracellular matrix (ECM) is the scaffolding from which bone derives much of its strength and architecture. Most molecules found within the ECM are produced by osteoblasts. The ECM contains nearly 30 types of collagen, as well as noncollagenous phospho- and glycoproteins. Type I collagen is the predominant form found within the ECM, making up approximately 90% of bone matrix. The significance of type I collagen is highlighted by patients with osteogenesis imperfecta (OI), a disease characterized by bone fragility and repeated fracture. OI often occurs in patients with pro- α 1 or pro- α 2-chain gene mutations, or from a mutation in one of the enzymes responsible for posttranslational hydroxylation of collagen.¹³⁶ In addition, bone mineralization takes place within the ECM. Bone mineralization is a well-orchestrated process during which hydroxyapatite crystals are laid down within the organic matrix of bone and calcify proteins that are secreted by osteoblasts.

In addition to type I collagen, many noncollagenous proteins are found within the ECM (Table 18.2). Osteopontin is a ubiquitous phosphoprotein that exists in multiple forms. It has been localized to most cells within bone, including osteoblasts, osteocytes, osteoclasts, and bone precursor cells.^{137–139} Osteopontin plays a role in the nucleation of hydroxyapatite crystals during matrix mineralization and also in osteoclast adhesion during bone remodeling.^{140–145}

Osteonectin is a glycoprotein that binds to calcium and type I collagen and also initiates and regulates bone mineralization.^{146,147} BSP is another important noncollagenous protein that, in contrast to osteopontin and osteonectin (both of which are expressed by many tissues throughout the body), is mainly expressed by cells within the skeleton.¹⁴⁸ BSP is an acidic phosphoprotein that binds to collagen and also promotes hydroxyapatite nucleation.¹⁴⁹ BSP-null mice express a phenotype characterized by small and undermineralized bones.¹⁵⁰

Osteocalcin (bone Gla protein) is a vitamin K-dependent γ -carboxyglutamic acid-containing protein, similar to factors II, VII, IX, and X of the coagulation cascade. The most abundant noncollagenous protein in bone, osteocalcin is secreted by osteoblasts and odontoblasts and is an important marker of increased bone turnover.¹⁵¹ Osteocalcin plays a role in bone turnover,^{152,153} osteoclast differentiation,¹⁵⁴ and energy metabolism.^{155,156}

Osteoblasts also produce proteoglycans, the most abundant of which is biglycan (BGN). BGN, a leucine-rich noncollagenous protein, is believed to play a role in the mineralization of bone given that *bgn*-deficient mice express an osteopetrotic phenotype.¹⁵⁷ However, BGN seems to play an important role

Table 18.2 Extracellular matrix molecules in bone

Molecule	Protein structure	Cell source	Present in nonosseous tissues	Function	Phenotype of knockout animals or deficiency in humans
Collagen type I	Trilaminar protein consisting of 2 α 1 chains and 1 α 2 chain	Many Mature and immature osteoblasts in bone	Yes	Primary scaffold of bone 90% of matrix	Osteogenesis imperfecta in humans
Alkaline phosphatase	Metalloenzyme	Mature and immature osteoblasts Different isoforms expressed by cardiac and hepatic cells	Yes	Enzyme Regulator of extracellular matrix mineralization Regulator of cellular migration, adhesion, and differentiation	Hypophosphatemia and defects in skeletal mineralization in knockout mice
Osteopontin	Phosphorylated glycoprotein	Osteoblasts/ osteoclasts Tumor cells (e.g., breast)	Yes	Osteoclast activation and extracellular matrix mineralization Anchor osteoclasts to mineralized matrix	Alterations in extracellular matrix remodeling in knockout mice
Osteonectin	Glycoprotein	Osteoblasts Endothelial cells, megakaryocytes	Yes	Binds calcium and collagen type I Regulator of mineralization	Unknown
Bone sialoprotein	Phosphorylated glycoprotein	Almost exclusively produced by skeletal cells (osteoblasts, osteocytes, hypertrophic chondrocytes)	No	Exact function unknown Regulator of cellular adhesion	Unknown
Osteocalcin	Vitamin K-dependent γ -carboxyglutamic acid-containing protein	Osteoblasts Odontoblasts Hypertrophic chondrocytes	No	Regulator of bone turnover Regulator of osteoclast migration Binds hydroxyapatite	Osteopetrosis in knockout mice
Biglycan	Proteoglycan	Mature and immature osteoblasts Nonosseous cells	Yes	Exact function unknown Regulates function apatite formation	Osteoporosis and small, thin, short limbs in knockout mice

outside the skeleton as well, as *bgn*-knockout mice manifest spontaneous aortic rupture and dissection,¹⁵⁸ dental and muscular abnormalities, thinning of skin, and osteoarthritis.¹⁵⁹

A variety of enzymes produced by bone cells also function within the ECM. The most prominent is ALP. Like osteocalcin, ALP is often used as a marker of bone turnover.¹⁶⁰ While the exact function of ALP is unknown, it is believed to be important for bone mineralization, during which it regulates apatite formation.

Principles of bone homeostasis and turnover

Unique to bone is its ability to undergo regeneration rather than repair with scar formation, as is typified by most

other tissues within the body. As described previously, bone is subject to constant remodeling, a process mediated by osteoclasts and osteoblasts. Physiologically, bone homeostasis is maintained by the counterbalancing of bone resorption with formation. When one of these processes becomes dysfunctional, patients may manifest a distinct pathology. Excessive bone resorption resulting in an excessive loss of bone is the fundamental pathogenesis underlying osteoporosis.¹⁶¹ Conversely, decreased bone resorption due to decreased osteoclast activity leads to an osteopetrotic phenotype.¹⁶² Decreased bone resorption due to increased osteoblast activity, however, will produce an osteosclerotic phenotype.

The structure of bone is a function of its material composition as well as the genetic blueprint of an individual. In addition, various loads to which bone is subjected define its

structure. This process of functional adaptation mediates repair of damaged bone and also facilitates prevention of damage before it may occur. Bone exhibiting suppressed remodeling and resorption suffers increased microdamage and fracture accumulation.^{163,164} It has been demonstrated that sites of microcracks are subsequently associated with new bone remodeling more often than expected by chance,^{165–167} which has led to the belief that bone remodeling and repair are often targeted to specific locations.¹⁶⁸

Wolff's law and mechanotransduction

Wolff (1892) derived a mathematical formula to describe how changes in the form and function of bone could lead to a change in its internal architecture and external structure.¹⁶⁹ Wolff believed that during the functional adaptation of bone to new loads that occur during one's life (e.g., as a result of trauma), the trabeculae within bone would reorient to align with the new principal stress trajectories of these environmental loads. Wolff's contributions were key to the early understanding of bone adaptation. More recently, authors have recognized that bones are subject to dynamic applied loads.¹⁷⁰

Considerable research has examined the initial events that stimulate bone adaptation. It is believed that the stimulus for bone remodeling is strain (the physical deformation of bone tissue).¹⁷¹ Osteocytes, the mediators of mechanotransduction,¹⁷² respond molecularly to mechanical loads. They undergo direct deformation by bending and also are deformed by the electrical potential induced by the flow of surrounding interstitial fluid.^{173,174} In addition, osteocytes are subjected to shear stress by the physical flow of interstitial fluid around their cellular membranes.^{175–179}

When strained, osteocytes convert the mechanical stimulus into chemical or electrical activity in a process thought to require various signaling molecules including NO and PGs.¹⁷² Interestingly, NO synthase, a calcium/calmodulin-dependent enzyme, is activated under conditions of increased intracellular calcium; intracellular calcium concentrations appear to increase in response to fluid flow.^{180,181} Klein-Nulend and colleagues¹⁸² demonstrated that a pulsating fluid flow model led to the release of NO from osteocytes. Taken together, these studies indicate that NO may be important in osteocyte mechanotransduction.¹⁸³ Additional studies have shown that pulsating fluid flow treatment also stimulates osteocytes to synthesize increased levels of PGE₂ and PGI₂,^{184,185} as well as increased levels of cyclooxygenase-2 (COX-2) mRNA.¹⁸⁶ COX-2 production is also stimulated by mechanical loading.^{187,188} Thus, COX-2 induction and the production of PGs are thought to be important mediators in the conversion of mechanical shear forces into signals that trigger bone turnover.

Bone regeneration: the role of the stem cell

In the last decade, the field of regenerative medicine has exploded with the discovery of new techniques to isolate cells capable of differentiating into many different tissues. In particular, the MSC (Fig. 18.3) has considerable therapeutic potential for fracture repair and other bone pathologies. For concordance, Dominici and colleagues¹⁸⁹ have proposed that MSCs meet the following criteria: (1) isolated MSCs must

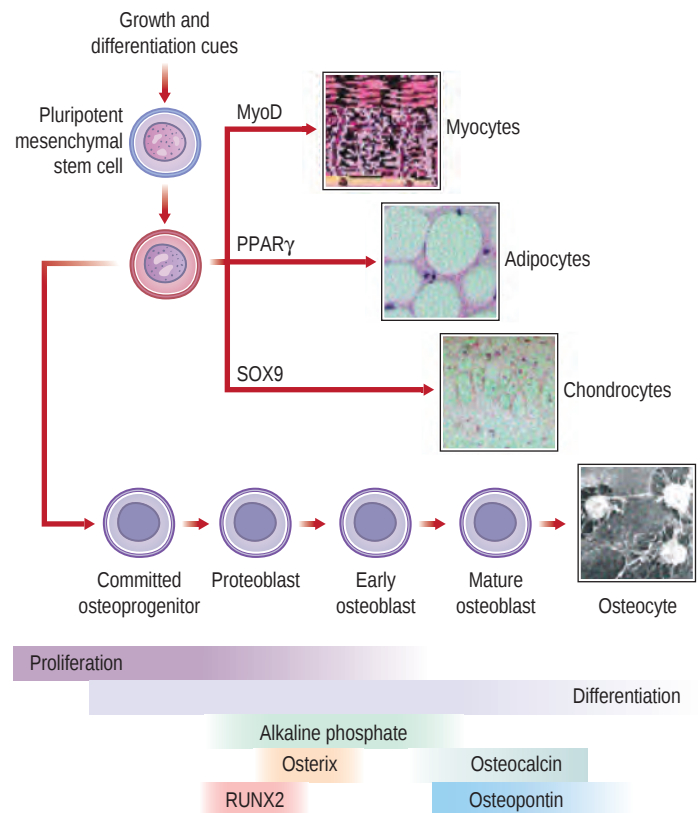


Fig. 18.3 Schematic representation of mesenchymal stem cell (MSC) differentiation pathways. MSCs are pluripotent stem cells that are capable of differentiating into several lineages with distinct growth and differentiation cues. These lineages include osteogenic, chondrogenic, adipogenic, and myogenic lineages. Lineage-specific differentiation is a well-coordinated process that is regulated by master regulators, such as MyoD for myogenesis, peroxisome proliferator-accepted receptor (PPAR)- γ for adipogenesis, SOX9 for chondrogenesis, and RUNX2 and Osterix for osteogenesis. Osteogenic differentiation can be staged by measuring alkaline phosphatase (early marker) and osteopontin and osteonectin (late markers). (From Tang N, Song W-X, Luo J, et al. Osteosarcoma development and stem cell differentiation. Clin Orthop Relat Res. 2008;466:2114–2130.)

adhere to plastic in culture; (2) MSCs should express the CD105, CD73, and CD90 surface antigens and not express the CD34, CD45, CD14 or CD11B, CD79A or CD19 and human leukocyte antigen-DR (HLA-DR) surface antigens; and (3) MSCs must have the capacity to differentiate into osteoblasts, adipocytes, and chondroblasts. MSCs and MSC-like cells are derived from bone marrow, but can also be expanded from skeletal muscle,¹⁹⁰ adipose tissue,¹⁹¹ dental pulp,¹⁹² the circulatory system,¹⁹³ synovium,¹⁹⁴ amniotic fluid,¹⁹⁵ urine,¹⁹⁶ the umbilical cord,¹⁹⁷ and fetal tissues.^{198,199}

The capability of MSCs to differentiate into and assist with the restoration and repair of bone has been extensively studied.^{200–203} MSCs are also used clinically in patients with various bone disorders.²⁰⁴ In a clinical trial²⁰⁴ that examined MSC administration to children with OI, bone mineral density, growth velocity, and ambulation all improved after MSC administration. However, the concentration of MSCs detected in bone, skin, and other tissues was less than 1%. These data and evidence from additional studies^{205,206} have led authors to postulate that MSCs may actually secrete soluble factors that alter tissue microenvironment, which may be an important mechanism by which MSCs repair tissue.^{207,208}

Molecular mechanisms of bone regeneration

Bone regeneration consists of a complex interplay of molecular processes that promote MSC migration, proliferation, and differentiation. Recently, there has been a great deal of research aimed at the identification of these molecular processes, and advances in our understanding of the molecular mechanisms of bone regeneration have been made. Many have been able to identify important signaling molecules as well as transcriptional regulators of bone regeneration (Table 18.3).

Bone morphogenetic protein

In the 1960s, Urist²⁰⁹ discovered the function of BMP from his work with demineralized bone matrix (DBM). To date, approximately 20 BMP isoforms have been characterized. BMPs are pleiotropic members of the TGF- β superfamily. BMPs, while important for brain and bone formation *in utero*,^{210–212} have generated much of their recognition from their osteoinductive properties. BMPs have also been implicated in human disease.²¹³

BMPs are synthesized as large precursor molecules that consist of characteristic subsections. A series of seven cysteine residues is located at the carboxyl termini of BMPs, and is important for proper protein folding. BMPs also contain a

signal peptide, a prodomain, and a mature peptide.²¹⁴ BMPs are thought to be secreted from cells in their active form.

BMPs are natural ligands for type I and type II serine/threonine kinase transmembrane cellular surface receptors. There are three type I and three type II receptors that are capable of binding BMPs.²¹² Upon ligand (BMP) binding, a heterotetrameric complex is formed, after which type II receptor kinase domains phosphorylate Gly-Ser domains in the type I receptor kinases. This process activates type I receptors to recruit and phosphorylate intracytoplasmic SMAD proteins (SMADs 1, 5, and 8). Following SMAD phosphorylation, SMAD 1, 5, or 8 will bind to SMAD 4, and this SMAD4-phosphorylated SMAD 1, 5, or 8 complex will relocate to the cell nucleus. Transcription factor activation occurs, leading to the transcription of bone morphogenetic target genes.^{215,216}

Bone morphogenetic protein function

BMP exerts pleiotropic effects throughout the lifespan of an organism. In the early stages of human development, BMP plays a key role in skeletogenesis.²¹¹ Also during this time period, BMP signals epidermal induction,²¹⁷ directs the development of neural crest cells,²¹⁸ and induces a sympathetic adrenergic phenotype.²¹⁹ Bmp-2-null mice typically die between 7 and 10 days of gestation due to cardiac defects, even before the formation of bone begins.

Table 18.3 Growth factors and fracture repair

Molecule	Ectopic bone formation	Segmental defect healing	Effect on fractures	Combination with other growth factors	Effective in lower vertebrates	Effective in primates	Potential clinical use
BMPs	Yes	Endochondral ++++ Membranous ++++	Increase callus volume Increase mechanical strength ? Increase rate of healing	Synergistic with TGF- β	Yes	Yes	Spinal fusion Alveolar bone deficiency Segmental defects Augment bone graft healing Dental implants
TGF- β	No	Endochondral ++ Membranous ++	Increases callus size Increases mechanical strength	Synergistic with BMP Increases FGF-2 expression Increases VEGF expression	Yes	No (limited study)	Role alone unclear
FGFs	No	Endochondral +/- Membranous +/-	Increase callus and bone volume Increase mechanical strength	Increase VEGF expression ? Synergistic with TGF- β	Yes	Yes (limited study)	Potential for augmenting angiogenesis in compromised wounds
PDGF	No	Endochondral - Membranous -	Increases callus volume Increases mechanical strength	Increases VEGF expression Synergistic with TGF- β for chemotaxis	Yes	No	Unknown

++++, very active; +/-, minimally active; -, no activity. BMPs, bone morphogenetic proteins; TGF- β , transforming growth factor beta; FGFs, fibroblast growth factors; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor.

BMP is the only signaling molecule capable of singly inducing *de novo* bone formation. It has been hypothesized that BMP-2, -6, and -9, and to a lesser extent, -4, and -7, various BMP isoforms, have the greatest osteogenic capacity.²²⁰ Luu and colleagues¹⁹ infected HEK293, C2C12, and C3H10T1/2 cells with adenoviral vectors containing various BMP isoforms (AdBMP). The authors measured the expression of early (ALP) and late (osteocalcin) osteogenic markers *in vitro*. They also assessed *in vivo* induction of heterotopic ossification by implanting AdBMPs into nude mice and evaluating radiographic and histologic results at 3 and 5 weeks. BMP-2, -4, -6, and -7 were shown to induce increased ALP elevation compared to other BMPs. In addition, BMP-2, -4, -6, -7, and -9 stimulated increased osteocalcin expression compared to others. The authors also found that BMP-2, -6, -7, and -9 induced the greatest degree of osteogenesis *in vivo*. The authors concluded that BMP-2, -6, and -9 have the greatest osteogenic potential, and that BMP-4, and -7 also have a significant degree of osteogenic potential.

BMP-2 promotes osteoblast differentiation by stimulating Runx2 in a process mediated by Smad proteins.²²¹ In addition, BMP-2 affects osteoblast differentiation via activation of the β -catenin signaling pathway.²²² Interestingly, endogenous activation of β -catenin induces ALP mRNA expression; however, BMP-2 must be present for β -catenin signaling to induce osteocalcin expression as well.²²³ Thus, β -catenin-dependent differentiation processes likely require BMP-2 to promote the later stages of osteoblast differentiation. Recently, it has been demonstrated that BMP-2-mediated osteoblast differentiation is also dependent upon Akt2 selective signaling.²²⁴ IGFs are important for osteoblast differentiation and normal bone growth,^{225–228} and Akt2 is a key molecule within the insulin signaling pathway. Mukherjee *et al.*²²⁴ showed that, although BMP-2 signaling is normal, osteoblast differentiation does not occur in Akt2-knockout mice. Delivery of Runx2 to Akt2-deficient mice restores osteoblast differentiation; thus, Akt likely serves a specific role in osteoblast differentiation through its regulation of Runx2 gene expression.

Furthermore, BMP-2 appears to improve healing of large osseous defects. Many studies have evaluated recombinant human BMP-2 (rhBMP-2) in *in vivo* animal models. In nonhuman primate and other mammalian models, rhBMP-2 has been shown to augment bone growth successfully and also close critical-sized osseous defects.^{229–231} The efficacy of rhBMP-2 in humans has also been assessed.^{232,233} Slosar *et al.*²³⁴ demonstrated that anterior lumbar allografts filled with rhBMP-2 experienced higher fusion rates than lumbar allografts without rhBMP-2 in patients who underwent lumbar fusion. The authors demonstrated that at 6 months and at 2 years, allografts with rhBMP-2 shortened the time-frame for expected improvement, and also improved patients' Oswestry Disability Index scores. Thus, it has been concluded allografts with rhBMP-2 can offer reliable and clinically significant benefits.

Adenoviral delivery of BMP (AdBMP) is also effective in stimulating osteogenic differentiation of mesenchymal progenitor cells. Our group isolated and subsequently reversibly immortalized primary murine calvarial cells that retained a progenitor cell phenotype.²³⁵ Immortalized calvarial cells (iCALs) treated with AdBMP-2 demonstrated an increase in early (e.g., alkaline phosphatase activity, osteocalcin mRNA transcription) and late (e.g., matrix mineralization) marker

expression of osteogenic differentiation compared to iCALs treated with AdGFP (control). Additionally, *in vivo* stem cell implantation assays revealed increased ectopic bone production from iCALs exposed to BMP-2 compared to control. In a similar study that evaluated the capacity of BMP-9 to induce osteogenic differentiation of calvarial progenitor cells, Teven and colleagues²³⁶ demonstrated that AdBMP-9-treated iCALs display enhanced osteogenic differentiation compared to AdGFP-treated cells (control) in both the *in vitro* and *in vivo* settings. The translational utility of these experiments relates to identifying effective agents for bony (e.g., calvarial) tissue regeneration. However, the clinical use of adenovirally-delivered BMPs has been limited and therefore further investigation is warranted.

Presently, rhBMP-2 (INFUSE, Medtronic, Inc.) is one of two rhBMPs approved by the Food and Drug Administration (FDA) for human application. The other is rhBMP-7 (rhOP-1). As described, rhBMP-2 is often used in spinal fusion, as well as orthopedic trauma and dental procedures. rhBMP-7 has shown clinical benefits in spinal fusion and tibia repair.^{237,238} Interestingly, although BMP-2 may be more osteoinductive than BMP-7 based on *in vitro* analyses,²⁹ there has been relatively little *in vivo* data comparing the two. Barr and colleagues²³⁹ have found that rhBMP-7 promotes similar bone quality but greater bone volume induction than rhBMP-2 in murine muscle pouch assays analyzed by microscopic computed tomography and histology. However, other studies have found different results.²⁴⁰ Conflicting results may be due to differences in experimental design.

Transforming growth factor- β

TGF- β has protean effects on cellular processes within the human body. TGF- β has been implicated in cell cycle regulation, angiogenesis, wound healing, and skeletogenesis. TGF- β also appears to have significant roles in human disease.²⁴¹ There are three distinct human TGF- β isoforms (TGF- β 1, - β 2, and - β 3). Though they exhibit differences, each isoform shares similar functions with one another, including functions pertaining to the regulation of osteogenesis and osseous repair.

TGF- β , like BMP, contains a cluster of conserved cysteine residues.²⁴² Each isoform is produced as a precursor molecule consisting of TGF- β and a propeptide region. In contrast to BMPs, however, TGF- β is secreted as an inactive molecule and stored in its latent form within the ECM. TGF- β becomes active after the noncovalent disulfide bond linking TGF- β and its propeptide region is broken.

There are four TGF- β receptors identified: types I, II, and III, and endoglin. TGF- β -initiated signaling, like BMP-mediated signaling, uses SMAD protein intermediates. Active TGF- β binds to either type III or type II receptors, both of which promote the phosphorylation of type I receptors. Phosphorylation of SMAD2 or SMAD3 follows, which in turn leads to the binding of SMAD4 to the phosphorylated SMAD2 or SMAD3 proteins. This complex translocates to the cellular nucleus, where transcription factors activate specific target gene transcription, thereby mediating the effects of TGF- β at the cellular level.

Evidence that TGF- β may play a role in osteogenesis has come from experiments demonstrating that TGF- β is produced by osteoblasts²⁴³ and stimulates the production of

collagen and osteopontin.^{244,245} *In vivo* studies have corroborated the osteoinductive effect of TGF- β .²⁴⁶ TGF- β 1, in particular, has been the subject of a considerable body of literature with respect to its osteogenic potential, in part because it is the dominant TGF- β isoform expressed by bone cells.²⁴⁷ *In vitro* analyses have demonstrated that TGF- β 1, by recruiting and stimulating the proliferation of osteoblast progenitors, increases bone formation.²⁴⁸ Interestingly, TGF- β 1 seems to have a differential effect on osteoblast differentiation. Early phases of differentiation appear to be promoted by TGF- β 1, while later phases are blocked.²⁴⁹

In addition, TGF- β 1 modulates the processes of osteoclastogenesis and bone resorption. At high TGF- β 1 concentrations (0.1–10 ng/mL), osteoclastogenesis appears to be downregulated.²⁴⁸ TGF- β 1 binds to its receptor on osteoblasts and augments the expression of OPG while also decreasing RANKL expression. A lower RANKL:OPG ratio results in maximal RANKL occupation by OPG, thus decreasing maturation of osteoclasts. TGF- β 1 appears to serve a bifunctional role, however, as low concentrations are associated with high levels of both RANKL and RANK, and subsequent osteoclastogenesis.

TGF- β 1 may also be important for the coupling of bone resorption and formation, as is found at bone resorption sites. Tang and colleagues²⁵⁰ injected green fluorescent protein (GFP)-labeled osteogenic bone marrow stromal cells (BMSCs) into the femur cavity of *Tgfb1*^{+/+} and *Tgfb1*^{-/-} immunodeficient mice. Using anti-GFP antibodies, injected BMSCs were detected at both 1 and 4 weeks. After 1 week, BMSCs were localized to the bone surfaces in *Tgfb1*^{+/+} mice; BMSCs were widely dispersed in the bone marrow (i.e., not at bone surfaces) of *Tgfb1*^{-/-} mice. After 4 weeks, BMSCs were embedded in trabecular bone in *Tgfb1*^{+/+} mice but not in *Tgfb1*^{-/-} mice. The authors concluded that TGF- β 1 plays an essential role in the coupling of bone resorption to bone formation by their induction of osteogenic BMSCs to sites of resorption.

In addition, TGF- β expression is elevated during fracture repair²⁵¹ and has been considered for exogenous use to augment bone growth and repair. Studies support that TGF- β isoforms significantly and rapidly induce the formation of endochondral bone at extracranial sites.²⁵² Studies on the effects of TGF- β on calvarial tissue are inconclusive. Many authors have found little osteoinductive potential associated with TGF- β .²⁵³ More recently, ectopic TGF- β was shown to augment calvarial defect healing in rabbits and promote normal suture reformation.²⁵⁴ Interestingly, combination therapy of BMP-2 and TGF- β did not demonstrate increased calvarial defect repair compared to either therapy individually.

Fibroblast growth factor

The FGF family is comprised of structurally related cytokines that mediate several physiologic processes including cellular proliferation, migration, and differentiation; mitogenesis; angiogenesis; embryonic development; and wound healing. There are at least 18 known members of the FGF family, all possessing a characteristically high affinity for heparin. Most isoforms share a similar internal core region that has important FGF receptor (FGFR)-binding properties.²⁵⁵ Mutations in FGFs or FGFRs are involved in the development of various skeletal dysplasias, including achondroplasia and

craniosynostosis.³⁸ Significant evidence exists demonstrating that FGF–FGFR signaling is essential to the developing axial skeleton. Additionally, the signaling cascade is necessary for cranial bone intramembranous ossification as well as for the maintenance of cranial suture homeostasis. A review of the roles of FGF signaling in physiologic development and in the development of skeletal diseases can be found elsewhere.²⁵⁶

There are four known FGFRs (FGFR-1, -2, -3, -4). Following FGF ligand binding, receptor dimerization occurs, which promotes the transphosphorylation of each receptor monomer by an intrinsic tyrosine kinase domain. Phosphorylated tyrosine residues on FGFRs become docking sites for adaptor proteins necessary for downstream signaling.²⁵⁷ Human gene studies have identified associations between skeletal disorders and FGFR mutations, including Pfeiffer syndrome (FGFR1), Crouzon syndrome (FGFR2), and achondroplasia (FGFR3).²⁵⁶

FGF has been implicated in a variety of osteogenic mechanisms. Coffin *et al.*²⁵⁸ found that increased concentrations of FGF-2 are found at epiphyseal growth plates of endochondral bone, specifically within the proliferation and hypertrophic zones. FGF-2 also accelerates fracture repair and closure of critical-sized defects.²⁵⁹ Interestingly, there seems to be a differential effect of FGF-2 treatment based on delivery. Continuous FGF-2 treatment stimulates osteoblast proliferation; however, it decreases levels of differentiation markers (e.g., ALP) and augments osteoclast formation, thus resulting in net bone resorption. In contrast, intermittent FGF-2 treatment enhances bone formation.

The effects of FGF-2 in combination with other growth factors have also been reported. Maegawa and colleagues²⁶⁰ examined MSCs deposited in osteogenic media supplemented with BMP-2, FGF-2, or both. MSCs supplemented by both FGF-2 and BMP-2 concurrently expressed the highest levels of ALP, osteocalcin mRNA, and bone matrix formation. In addition, Sabbieti *et al.*²⁶¹ investigated whether FGF-2 modulates the anabolic response of bone to PTH. Primary calvarial osteoblasts were isolated from *Fgf-2*^{+/+} (wild type) and *Fgf-2*^{-/-} mice. By immunocytochemistry, *Fgf-2*-null osteoblasts expressed decreased Runx2 protein synthesis as well as significantly less Runx2 expression within perinuclear and nuclear spaces than wild-type variants when exposed to PTH. Given the importance of Runx2 on osteogenesis, it was concluded that *Fgf-2* expression is required for PTH to promote an anabolic response by bone.

Platelet-derived growth factor

Platelet-derived growth factor (PDGF) plays an important role in a number of biological processes, including embryological development, inflammatory reactions, angiogenesis, organogenesis, and wound healing. Four unique isoforms of PDGF have been characterized (PDGF-A, -B, -C, -D), which are inactive in their monomeric forms, and thus must dimerize to become active. Five dimeric PDGF compounds have been identified (PDGF-AA, -BB, -CC, -DD, and -AB).²⁶² All PDGF molecules share a highly conserved PDGF/vascular endothelial growth factor (VEGF) homology domain, a motif also found in VEGF.²⁶³ PDGFs interact with two receptor tyrosine kinases (PDGF receptor- α (PDGFR- α) and PDGFR- β), which also must dimerize to activate.²⁶⁴ Receptor

dimerization results in autophosphorylation at a specific tyrosine residue on a PDGFR, a necessary step for signal transduction to proceed. Because of unique temporospatial expression patterns, it is believed that PDGFR- α and PDGFR- β mediate distinct events during development.²⁶⁵

PDGF is a potent mitogen and chemotactic agent for cells and tissues of mesenchymal origin and is crucial in bone homeostasis and repair. At sites of bone fracture, platelets congregate and release PDGF. PDGF attracts many other cell types important for tissue repair and the formation of granulation tissue. PDGF has also been shown specifically to attract osteogenic cells derived from calvaria, periosteum of long bones, trabecular bone, and BMSCs.²⁶⁶ Additionally, angiogenesis is crucial for bony healing (to be discussed later) and PDGF, in addition to its direct mitogenic effect on osteoblasts, indirectly enhances bone regeneration by stimulating angiogenic cytokines.²⁶⁷

PDGF also stimulates bony healing via interactions with other growth factors. Levi *et al.*²⁶⁸ showed that IGF-1 exposure promoted osteogenic differentiation of human adipose-derived stromal cells but PDGF-A alone did not. In combination, IGF-1 and PDGF-A enhanced osteogenesis to a greater degree than IGF-1 alone, possibly due to enhanced IGF-1 transcription in the presence of PDGF-A.

The effects of PDGF on osseous repair in the clinical setting have recently been investigated. One randomized controlled trial assessed the effectiveness and safety of administering recombinant human PDGF-BB (rhPDGF-BB) with beta-tricalcium phosphate (β -TCP) for periodontal osseous defects.²⁶⁹ Compared to β -TCP, β -TCP in combination with rhPDGF-BB significantly enhanced linear bone growth (LBG) and percent defect fill at 6 months. Subjects receiving rhPDGF-BB also demonstrated a significant gain of clinical attachment level (CAL) versus those who did not. These early data were promising and therefore the authors extended the study to test long-term stability and efficacy of PDGF-BB. After 36 months, an analysis of 83 subjects with localized severe periodontal osseous defects demonstrated that, based on composite outcomes for CAL gain and LBG, PDGF-BB in a synthetic scaffold matrix promotes long-term stable clinical and radiographic improvements.²⁷⁰ Another randomized pilot study offered rhPDGF-BB within a β -TCP matrix to patients in need of ankle/hindfoot fusion.²⁷¹ Compared to subjects receiving autologous bone grafting, the PDGF group demonstrated greater osseous bridging across the fusion site.

Healing of fractures

Bone repair is the physiologic process by which the body facilitates the healing of fractures. In many ways, fracture repair recapitulates the events that occur during skeletogenesis. Successful fracture healing is dependent upon many factors. The mechanism of disruption, the fracture pattern, and the method and timing of fixation all affect the outcome of bone repair. For example, fractures that create more than two fragments of the same bone (comminuted fractures) require swift surgical intervention to heal successfully. In addition, the biologic milieu surrounding a fractured bone may play a role in the fate of the fracture.

Originally distinguished based on their histology, two types of bone repair have been described (Fig. 18.4). Primary

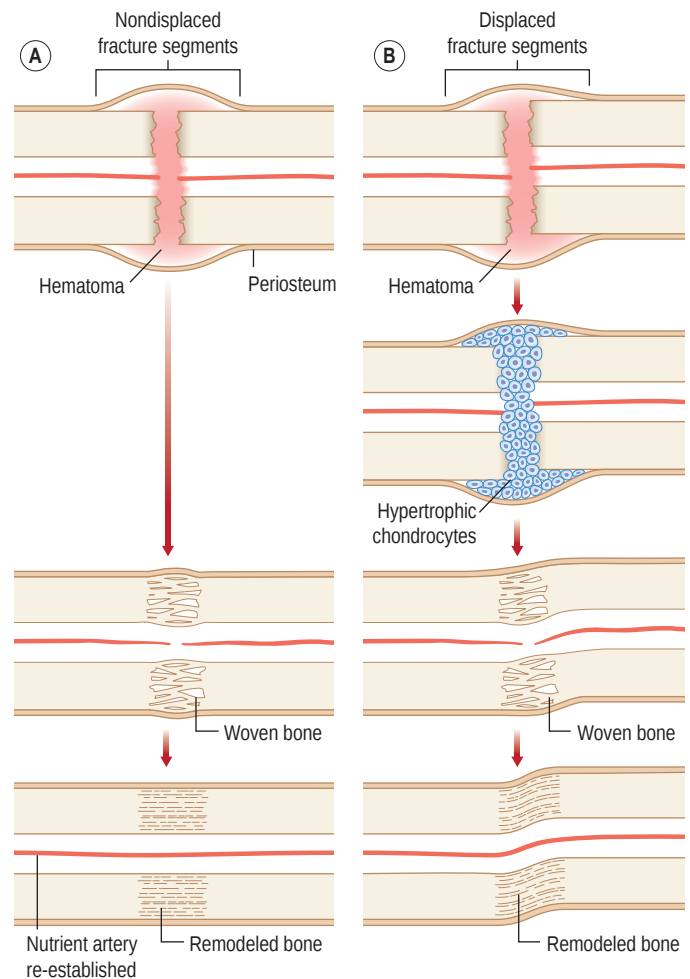


Fig. 18.4 Schematic representation of primary and secondary (callus) bone repair. (A) Primary bone repair: nondisplaced bone fragments heal without cartilaginous intermediate. (B) Secondary (callus) bone repair: displaced (or unstable) bone segments heal with cartilaginous intermediate. (Modified from Mehrara BJ, McCarthy JG. *Repair and grafting of bone*. In: Mathes SJ, ed. *Plastic Surgery*. Vol. 2. Philadelphia: WB Saunders; 2005:639–718.)

bone repair refers to direct cortical healing of two fracture ends without a cartilaginous intermediate. In contrast, during secondary (callus) bone repair, a cartilaginous intermediate is formed by mechanisms that occur within the periosteum, soft tissues, and bone marrow. Most fracture repair is by secondary bone healing.

Primary bone repair

Primary bone repair involves the direct deposition of woven bone by osteoblasts to re-establish mechanical continuity between fracture fragments. Similar to intramembranous ossification, the periosteum provides osteoprogenitor cells and undifferentiated MSCs during primary bone repair. In order for primary repair to occur, fracture fragments are reduced to anatomic position, usually by rigid internal fixation. The interfragmentary strain should also be at a minimum.²⁷² Bone healing occurs under axial compression and fails under tension (Fig. 18.5).

During primary bone repair, new bone is synthesized in parallel to the long axis of the bone by osteoprogenitor cells. This process is initiated by the formation of cutting cones at

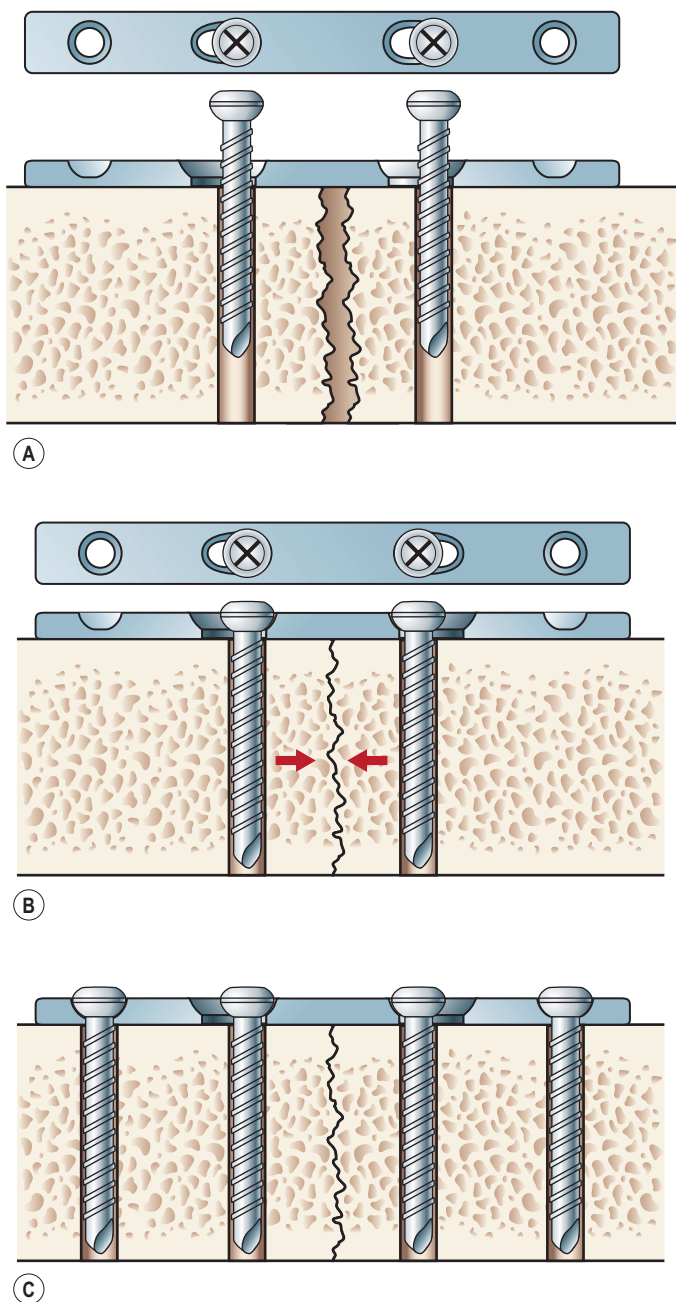


Fig. 18.5 The compression mode of miniplate fixation. **(A)** A four-hole plate. Note that the inner holes are eccentrically shaped so that, as the screws are tightened, the head falls into the wider portion and compresses the bone margins **(B)**. **(C)** Completed view of the skeletal fixation.

the junction of live and necrotic skeletal segments. A cutting cone is a system of cells, mainly composed of active osteoclasts. It burrows its way through cortical bone across the fractured bone segments, thereby allowing the ingrowth of blood vessels and undifferentiated MSCs. MSCs then differentiate into bone-producing osteoblasts. New haversian systems are created and provide pathways for blood vessel penetration. Initially, bone is laid down in a woven-matrix configuration. Within a few weeks, the woven bone becomes more lamellar-like in its orientation. As the proportion of lamellar bone increases over the course of months, complete fracture repair occurs. The benefits of rigid plate osteosynthesis include increased stability, decreased incidence of non- and

malunion, and decreased incidence of infection.²⁷³ Orthopedic and cardiac surgeons commonly perform rigid internal fixation.²⁷⁴ Reconstructive surgeons also use rigid fixation techniques to repair or reconstruct the craniofacial skeleton.^{275,276}

Secondary (callus) bone repair

Untreated fractures or those treated with external or intramedullary fixation or by sling or cast immobilization (i.e., without rigid fixation) heal by secondary repair. During secondary or callus bone repair, colonies of MSCs form cartilage at the fracture prior to bone formation. There are three overlapping phases of secondary repair: inflammatory, reparative, and remodeling (Fig. 18.6). However, at least five distinct stages have been described.²⁷⁷

After a fracture, the disruption of osseous, soft, and vascular tissues initiates the inflammatory phase. Lasting roughly seven days, the inflammatory phase peaks at approximately 48 hours post-injury. Pain and swelling during this time promote immobilization at the fracture site.²⁷⁸ A hematoma forms, further immobilizing the area via its fibrin network. The hematoma is also a source of signaling molecules that initiate repair.²⁷⁹ Platelets release PDGF and TGF- β , which promote MSC proliferation and osteogenic differentiation. Recruited neutrophils, lymphocytes, monocytes, and macrophages remove necrotic debris and stimulate angiogenesis.

Approximately 3–4 days post-fracture – before the inflammatory phase subsides – the reparative phase commences. This phase lasts weeks to months and is characterized by the development of a fracture callus that will stabilize and unite fracture segments before being replaced by bone. The callus is chiefly composed of cartilage, but also contains woven bone, osteoid, fibrous connective tissue, and blood vessels. MSCs from the surrounding periosteum and marrow migrate to the injured site and mature into many cell types, including osteoblasts, chondrocytes, and fibroblasts, which form the callus.

The fracture callus undergoes both intramembranous and endochondral ossification.²⁷⁷ Endochondral ossification occurs during the second week of repair, when abundant cartilage overlying the fracture site (formed by chondrogenesis of the callus) undergoes calcification. Blood vessels grow into this calcified cartilaginous callus, bringing with them osteoblast progenitor cells. As the calcified cartilage is resorbed by chondroclasts, osteoblasts begin to lay woven bone. Intramembranous ossification, on the other hand, occurs adjacent to the fracture site.

The remodeling phase is characterized by the replacement of woven bone with lamellar bone and may remain active for several years. Osteoclasts resorb poorly located trabeculae and new bone is formed along the lines of stress. In response to varying mechanical loads, bone will gradually modify at the fracture region until optimum regeneration is achieved. During remodeling, pain subsides and the normal activities can be resumed.

Variables influencing bone repair

Blood supply

Blood flow to bone represents approximately 10–20% of total cardiac output. The pattern of vascularization to the majority of the appendicular skeleton is similar in organization to the

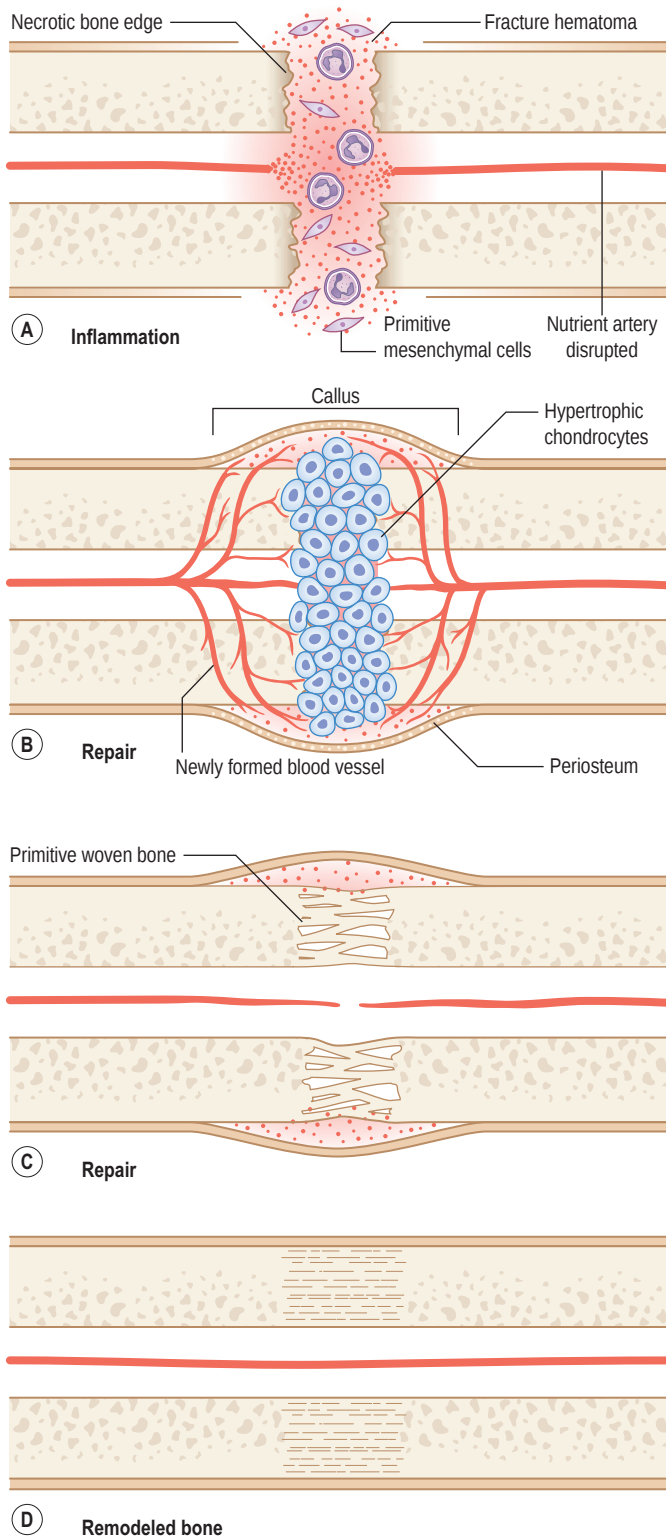


Fig. 18.6 Schematic diagram of callus fracture repair in endochondral bone. **(A)** Early stages of fracture repair characterized by hematoma formation, inflammatory cell migration and differentiation (polymorphonuclear neutrophils), and scattered primitive mesenchymal cells. **(B)** As healing progresses, a callus is formed between the bone edges, and hypertrophic chondrocytes can be seen. In addition, newly formed blood vessels sprout from the nutrient artery and local blood vessels. **(C)** Primitive woven bone has bridged the fractured bone segment. **(D)** Woven bone is remodeled into lamellar bone.

vascular pattern of a typical long bone.²⁸⁰ A tubular long bone in the adult human receives blood by three distinct arterial systems that interconnect extensively with one another (Fig. 18.7). The primary blood supply to the inner two-thirds of bony cortex and the medullary cavity comes from the diaphyseal nutrient artery. As the nutrient artery traverses the cortex, it passes through to the medullary cavity, where it divides into ascending and descending medullary branches. Metaphyseal and epiphyseal arteries represent the second significant source of blood. These vessels arise from arteries supplying adjacent joints and deliver blood to cancellous bone found at the end of long bones. The third main source of blood comes from periosteal arteries, which carry supply to the outer one-third of cortex.

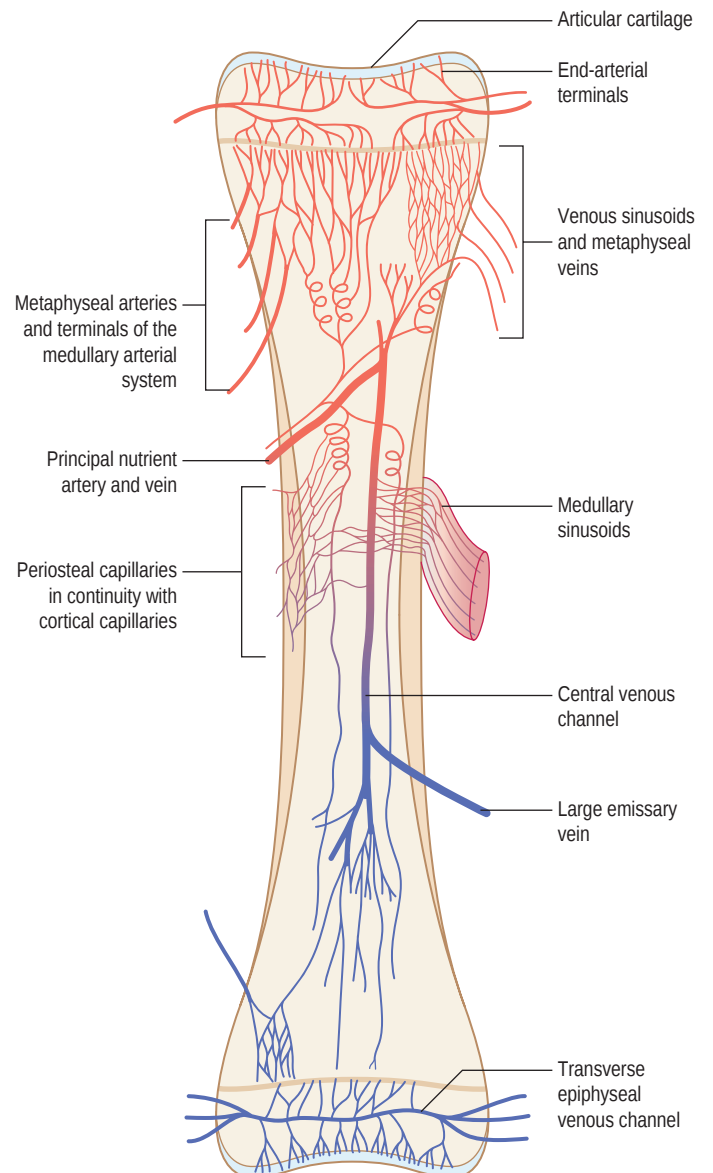


Fig. 18.7 The three sources of blood supply to the long bone. The nutrient artery provides the principal source of blood supply to the marrow cavity and the inner cortex. The diaphyseal periosteal vessels supply the outer cortex of the diaphysis. The metaphyseal epiphyseal periosteal vessels penetrate the cortex of the bone in the adult and anastomose with the nutrient artery, providing adequate supply to the marrow cavity and inner cortex in cases of disruption of the nutrient artery.

As blood travels through bone from endosteum to periosteum, it flows through sinusoids and arterioles within the haversian system. Exchange vessels (i.e., vessels connecting the arterial and venous systems) within osteons lie parallel to the axis of the bone. Collecting sinuses and veins with similar names to their arterial counterparts receive deoxygenated blood from exchange vessels. A high intramedullary pressure

is likely responsible for the centrifugal flow of blood through bone.²⁸¹

Angiogenesis is critical for bone maturation and repair.²⁸² Although the mechanisms that regulate angiogenesis during fracture repair have not been fully elucidated, many important angiogenic cytokines have been described (Table 18.4). One molecule thought to play a pivotal role in angiogenesis within

Table 18.4 Growth factors and angiogenesis

Growth factor	Structure	Angiogenesis	Function	Role in fracture healing	Regulation of expression	Receptor
BMP	Single large propeptide molecule Cleavage enables dimerization Member of the TGF- β superfamily Conserved series of seven cysteine residues at carboxyl terminal At least 15 known isoforms	Indirect regulator of angiogenesis	Mitogen and chemoattractant for osteoblasts and mesenchymal cells Apoptosis Patterning	Expressed by mesenchymal cells early in fracture repair Also expressed by osteoblasts and osteoclasts Exogenous BMPs can heal critical-sized defects Ectopic bone formation ? Accelerate fracture repair ? Actions synergistic with TGF- β	Patterning genes and transcription factors (e.g., Cbfa1)	Serine-threonine kinase receptors
TGF- β	Propeptide Cleavage necessary for activation At least three different isoforms	Indirect regulator of angiogenesis	Chemoattractant and mitogen for osteoblast precursors and osteoblasts Inhibits osteoblast differentiation Regulates expression of other growth factors important in angiogenesis and osteogenesis Increases matrix synthesis	Produced for osteoblasts, mesenchymal cells, osteoclasts Increases callus formation and volume Subperiosteal injection promotes both chondrogenesis and membranous ossification Exogenous TGF- β may heal some critical-sized defects	Patterning genes and transcription factors Mechanical strain	Serine-threonine kinase receptors
FGF-2	Heparin-binding glycoprotein At least nine different isoforms	Direct regulator of angiogenesis	Angiogenesis Regulator of bone development and skeletal patterning Can regulate osteoblast differentiation and proliferation (actual effect is dose-dependent)	Increases angiogenesis in fracture site Increases expression during fracture repair Exogenous FGF-2 can increase mechanical strength of fractures ? Accelerates fracture repair or promotes healing of critical-sized defects	Inflammatory cells and acute inflammation Patterning genes and transcription factors	Tyrosine kinase receptors

Table 18.4 Growth factors and angiogenesis—cont'd

Growth factor	Structure	Angiogenesis	Function	Role in fracture healing	Regulation of expression	Receptor
VEGF	Dimeric glycoprotein	Direct regulator of angiogenesis	Increases vascular permeability Increases vascular sprouting Increases endothelial cell migration, proliferation, adhesion	Increased expression during fracture repair Expressed by osteoblasts, osteoclasts, and mesenchymal cells Increases blood vessels in growth during fracture repair	Microenvironment (e.g., pH, hypoxia, lactic acid concentration) Growth factors (e.g., TGF- β , FGF, BMP, IGF), inflammatory cytokines (e.g., PGE ₂)	Tyrosine kinase receptors
PDGF	Dimeric, disulfide-bonded polypeptide chain α and β subunits determine isoform (AA, AB)	Indirect regulator of angiogenesis	Promotes chemotaxis of osteoblasts and inflammatory mediators Decreases cellular differentiation Increases collagen synthesis Increases collagen degradation and turnover May promote osteoblast proliferation	Released by degranulating platelets and acts to increase osteoblast chemotaxis, and possibly proliferation Expressed by osteoblasts, macrophages, and mature/immature chondrocytes during fracture repair Promotes synthesis of angiogenic molecules (e.g., VEGF) Promotes matrix deposition and turnover	Inflammation and injury Mechanical strain TGF- β (decreased expression)	Tyrosine kinase receptors

BMP, bone morphogenetic protein; FGF-2, fibroblast growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PGE₂, prostaglandin E₂; TGF- β , transforming growth factor-beta; VEGF, vascular endothelial growth factor.

developing and healing bone is VEGF. Other factors described previously (BMP, TGF- β , FGF-2, and PDGF) have also been implicated in angiogenic processes necessary for osteogenesis. VEGF and FGF-2 are the only two directly acting regulators of angiogenesis; other growth factors serve indirect roles. In addition, the hypoxia-inducible factor-1 α (HIF-1 α) pathway is crucial to the coupling of angiogenesis with osteogenesis.²⁸³ Discoveries associated with this pathway have led authors to hypothesize that skeletal angiogenesis and osteogenic-angiogenic interactions are rate-limiting processes in bone growth.

A potent regulator of both vasculogenesis and angiogenesis, VEGF mediates many important functions during the embryologic stage of development and throughout the lifetime of organisms. Deletion of a single VEGF allele is associated with lethality *in utero*.²⁸⁴ VEGF is structurally related to PDGF and is expressed by many cell types, often at high concentrations within highly vascularized tissues. VEGF mediates its effects on cells through interactions with VEGF receptors (VEGFR-1, VEGFR-2, VEGFR-3).

The hypothesis that VEGF plays an essential role in skeletogenesis mainly comes from studies examining endochondral bone formation. At the epiphyseal growth plates of long bones, hypertrophic chondrocytes express high levels of VEGF.²⁸⁵ Injection of an anti-VEGF monoclonal antibody

results in inhibition of vascular invasion of the nonhuman primate growth plate, thereby hampering longitudinal bone growth.²⁸⁶ Moreover, mice treated with a VEGF inhibitor manifest significantly decreased bone capillary invasion and trabecular bone formation.²⁸⁷ Cessation of anti-VEGF treatment is associated with capillary invasion and restoration of bone growth. A comprehensive review produced by Yang *et al.*²⁸⁸ discusses VEGF in the context of bone angiogenesis and development, emphasizing its role on intramembranous and endochondral ossification.

The therapeutic utilization of VEGF and other angiogenic cytokines is a subject of great promise in the treatment of patients with both complicated and uncomplicated fractures. Luo and colleagues²⁸⁹ examined the effects of VEGF and BMP-2 on bone defect repair around dental implants. The study found that bone marrow stromal cells within chitosan/collagen scaffolds were responsive to AdBMP-2 administration but VEGF alone failed to stimulate bone formation. Administration of AdBMP-2 and VEGF protein together resulted in significantly increased bone formation and bone-to-implant contact compared to the AdBMP-2 group, suggesting a synergistic effect of combination BMP-2 gene and VEGF protein therapy on bone healing. In addition, Liu and Olsen²⁹⁰ found that mice with a congenital deficiency of VEGF in osteoblastic precursor cells demonstrate reduced bone mass

and increased bone marrow fat consistent with an osteoporosis-type phenotype. Therefore, VEGF has become a potential target for therapies to reduce bone loss.

Fracture fixation

Critical to the success of fracture repair in long bones is the extent of movement at the fracture site after fixation.²⁹¹ Delayed union and nonunion are both associated with excess motion; however, some movement, known as micromotion, can enhance bone healing. The mechanism by which absolute immobilization hampers fracture repair may be related to increased resorption in a stress-protected environment. In addition, the degree of mechanical strain endured at the site of a fixed fracture has differential effects on chondrogenesis and osteogenesis.²⁹²

Age

Characteristic changes within bone occur during the aging process. Pediatric fractures tend to heal at an accelerated rate compared to adult fractures.²⁹³ This may in part be due to the effect of age on angiogenesis.²⁹⁴ To understand this, Lu and colleagues²⁹⁵ evaluated tibial fractures created in 4-week-old, 6-month-old, and 18-month-old (juvenile, middle-aged, and elderly, respectively) rats. At 7 days post-fracture, there was a higher surface density of blood vessels in juvenile fracture calluses compared to middle-aged and elderly rats. In addition, juvenile rats expressed increased HIF-1 α and VEGF at 3 days post-fracture versus older rats. These data support the notion that angiogenic potential during fracture healing changes over time. Age may also influence fracture repair via effects on periosteal structure, cell population and chondrogenic potential; stem cell function; and biologic signaling.^{296,297}

Bone remodeling

Osteoinduction

Osteoinduction is a process by which undifferentiated pluripotent cells are stimulated to become cells within the osteoblast lineage.²⁹⁸ It occurs naturally during skeletogenesis and fracture repair.

Although osteoinduction is an intrinsic biologic process, it can also be manipulated exogenously. For example, purified and recombinant human isoforms of BMP are commonly used in experimental settings to induce bony formation. Various biomaterials have also been used for the same purpose. Bioglass and other osteoinductive materials have shown promise when used in craniomaxillofacial applications.²⁹⁹ After bioactive glass is mixed with saline or blood, an apatite surface layer forms at the biomaterial–bone interface, which incorporates collagen and proteins from surrounding native bone. In addition to producing a chemical bone at the interface, the apatite layer stimulates production of osteogenic cytokines from surrounding osteoprogenitor cells, resulting in new bone formation.³⁰⁰

A major concern in the treatment of significant osseous defects is the amount of native tissue available for repair. Large defects may not be amenable to autologous reconstruction without undue donor site morbidity. Therefore, an area of intense study is the identification of undifferentiated cells that

differentiate to produce bone when exposed to osteoinductive factors. Significant quantities of these progenitor cell types are found in adipose tissue¹⁹¹ as well as the neonatal umbilical cord and infant palatal periosteum.³⁰¹ The ability to harvest and manipulate these cells via osteoinduction has important therapeutic implications for both children and adults suffering critical-sized bony defects.

There are numerous strategies to facilitate the osteoinduction of effector cells in order to produce bone. Examples include the use of bone grafts, vascularized bone flaps, bioactive scaffolds, osteogenic growth factors, and biophysical stimulation.³⁰² A detailed discussion of bony regeneration and osteoinduction can be found elsewhere.^{303,304}

Osteoconduction

Osteoconduction is the ability of a material to serve as a scaffold onto which bone can attach and grow. During primary bone repair, the opposing fracture fragments mediate osteoconduction. In secondary bone repair, callus ECM acts as a scaffold onto which new bone can attach and develop. In the field of regenerative medicine, many implanted materials serve an osteoconductive role. An osteoconductive substrate must be porous to allow for the ingrowth of bone and fibrovascular tissue during osteoinduction.³⁰⁵ Many osteoconductive materials are available to enhance bony healing in the clinical setting. Reconstructive surgeons can choose from allografts (processed human bone), autogenous bone grafts, purified collagen, calcium phosphate (CaP) substitutes, synthetic polymers, and more. In some cases, osteoconductive materials may also have osteoinductive properties. Native bone, for example, stimulates both osteoconduction and osteoinduction. Additionally, purely osteoconductive materials (e.g., CaP substitutes) are enhanced by being combined with osteoinductive factors (e.g., BMP) before placement into a defect.³⁰⁶

Osseointegration

The phenomenon of osseointegration describes a stable anchorage between bone and implant that results in a structural and functional connection between the two. Similar to primary fracture healing, during osseointegration native bone and the implant unite without a cartilaginous intermediate. A key difference between primary fracture repair and osseointegration is unification of native tissue and a foreign body during osseointegration. Therefore, the structure and composition of the implant are integral to the process.

In order for osseointegration to manifest, certain prerequisites must be met.³⁰⁷ The implant must be bioinert or favorably bioactive. Bioinert materials do not cause adverse reactions in native tissue. Titanium is an example of a bioinert material often used in dental, craniofacial, and orthopedic procedures. A material that is favorably bioactive promotes a positive tissue reaction by facilitating osseous tissue production or chemical bond formation between implant and native tissue. Favorable bioactive agents are often used to coat implants with an otherwise unfavorable mechanical quality. The degree and strength of bone–implant contact depend on the surface properties of an implant. The extent of bone–implant interface has been shown to be positively correlated to implant surface roughness.³⁰⁸ A rougher implant may be better able to tolerate

shear stress. In addition, Butz and colleagues³⁰⁹ assessed the intrinsic biomechanical properties (hardness and elastic modulus) of bone tissue integrated to titanium implants with varying degrees of surface roughness. Bone deposited around acid-etched titanium implants displayed enhanced biomechanical properties compared to bone deposited around implants with smoother, machined surface topography. Similarly, compared with machined surfaces, implant surfaces subjected to anodization exhibit increased bone-to-implant contact.³¹⁰

Distraction osteogenesis

Distraction osteogenesis, the formation of new bone from the gradual separation of osteotomized fronts, was pioneered by the work of Codvilla at the turn of the 20th century and expanded by Ilizarov in orthopedic surgery.^{311–313} Through a set of rigorous experimentations, Ilizarov³¹³ was the first to establish the hypothesis that gradual controlled separation of osteotomized bone results in a “tension stress effect” leading to angiogenesis and new bone formation. These initial observations and classic experiments were based upon the axial skeleton. It was not until the early 1970s that the concept of craniofacial distraction was introduced, first in a canine model,³¹⁴ in which the authors demonstrated correction of an iatrogenic crossbite by an external distraction device (1 mm/day for 2 weeks). The application of distraction to the human craniofacial skeleton was finally introduced by McCarthy *et al.* in the early 1990s.^{315–317} Since its inception in the human mandible, the indications of distraction osteogenesis have expanded from congenital cases to cases of craniofacial skeletal deficiency with tumor-, trauma-, or iatrogenic-related etiologies.

Distraction osteogenesis requires three main stages for successful augmentation of bone formation: latency, activation, and consolidation. The first stage, latency, occurs immediately after osteotomy and refers to the period during which bone healing is initiated at the bony gap, periosteal integrity is restored, and callus formation begins. Latency typically ranges between 1 and 7 days, and is typically gauged according to the patient's age; the younger the patient, the shorter the latency period. During the second stage, activation (distraction), osteogenesis is induced with the generation of immature bone. Distraction occurs by the turning of an axial screw at a predetermined rate for a certain number of days until target bone augmentation is achieved. The third and final stage, consolidation, refers to the phase during which immature bone remodels into mature bone. In practical terms, consolidation is the period from the end of distraction to the removal of the device. The parameters for these stages are established by the craniofacial surgeon in response to specific patient profiles and the region of the skeleton undergoing distraction.

As understanding of and experience with distraction osteogenesis advance, associated adverse events occur less frequently.³¹⁸ However, this number may be underreported.^{319,320} Complications that arise may be due to surgeon technique, patient factors (see below), hardware failure, or unknown factors. Many authors have attempted to classify complications for specific body areas (e.g., mandibular distraction)^{318,320–322}; however, no consensus standard classification scheme exists.

Histology

Successful distraction osteogenesis results from membranous ossification in the absence of a cartilaginous intermediate.^{323–327} In the early phases of regenerate formation, distraction angiogenesis is a more accurate term to describe the cellular response to ischemia and traction. This phase is characterized by the appearance of multipotent precursor cells and type I collagen matrix expression in the distraction zone. Recently, Cetrulo and colleagues were able to demonstrate the honing of MSCs to the distraction zone in rat mandibles after intra-arterial transfer,³²⁸ an indication that paracrine factors expressed in ischemia (e.g., HIF-1 α) are chemoattractants and eventual agents of osteoinduction. Specifically, endothelial precursor cells are enriched at midactivation through 1–2 weeks into the consolidation period, when distracted rats were compared to controls.³²⁸ CD31, CD34, and Flk-1, markers of neovascularization, stem cells, and endothelial precursors, respectively, have all been demonstrated by immunohistochemistry. Further in the activation period, dense collagen fibrils are formed and organized in the direction of distraction as a template for mineralization.^{325,329–331}

It has been recognized that bone precursor cells respond to mechanical cues in order to differentiate. Distraction appears to be no exception to this tenet. In a rat model, Rhee and colleagues demonstrated increased intranuclear expression of signal transduction factors ERK1/ERK2 early in the distraction phase.³³² This expression paralleled upregulation of BMP-2/BMP-4, two relatively potent osteoinduction agents. Mineralization by active mature osteoblasts starts 10–14 days after the onset of distraction, and begins at the osteotomy fronts, proceeding centrally towards the relatively avascular fibrous interzone (Fig. 18.8).^{313,325,329,333} This leads to the formation of the primary mineralization front. Thin-walled vascular channels and bony spicules are slowly converted to normal lamellar bone and marrow. Interestingly, during the latter phase of activation, the infantile regenerate is still malleable and can remodel according to external forces. One can therefore take advantage of the gradual process and judiciously manipulate the distracted bone clinically in order to obtain a more precise occlusion, for example. This clinical principle, which is based on the gradual histomorphogenesis of the distraction zone, is termed molding the regenerate.^{334,335} Several studies have confirmed that molding the distraction bone, clinically by use of an orthopedic appliance, does not lead to disturbance of the regenerate or fibrous nonunion.^{334,335}

Variables affecting osteogenesis

To understand the variables that have a negative or positive impact on osteogenesis in the context of distraction, one must understand the factors that promote successful regenerate formation and bony union. These tenets are aptly described by Ilizarov³³⁶: (1) device stability; (2) a latency period; (3) a gradual distraction (activation) period; and (4) a sufficient consolidation period. First, osteocyte viability reflects osteoblastic activity and thus the selection of a strong area of bone for osteotomy and distractor placement is critical. A stable device placed in stably healing bone results in the formation of strong cortical bone within the regenerate and minimizes the chance of fibrous nonunion. It follows that any thermal or mechanical injury to the bone can damage the blood supply to the bone, resulting in

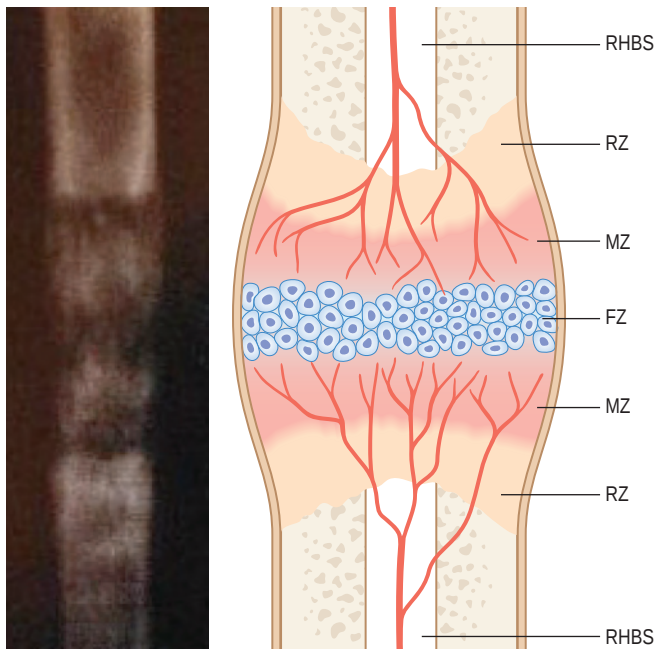


Fig. 18.8 Schematic drawing of bone formation during distraction osteogenesis. After approximately 10 days of distraction and during the distraction period, the regenerated tissue can be divided into three zones: (1) an avascular fibrous interzone (FZ); (2) two mineralization zones (MZ) or fronts; (3) and two regenerate zones (RZ). Regenerate zones are adjacent to residual host bone segments (RHBS). (From Samchukov ML, Cope JB, Cherkashin AM. *Craniofacial Distraction Osteogenesis*. St. Louis: Mosby; 2001.)

ischemic fibrogenesis. Fibrogenic damage leads to irregular and disorganized collagen formation from arterial insufficiency or cystic degeneration from venous outflow obstruction. Previous concerns of periosteal damage resulting in poor osteogenesis have recently diminished as increasing experience among craniofacial surgeons has demonstrated that, even with complete osteotomy, the periosteum is sufficiently osteogenic for strong bone production.

Inappropriate timing of the distraction stages can result in osteogenic failure. In terms of the latency period, this translates into either too short a period (immediate distraction) or a prolonged period (delayed distraction). Important for primordial callus and ultimately regenerate volume, latency periods range between 0 and 7 days, depending upon patient variables, such as age, osteotomy site, blood supply, and other factors that may affect regenerate formation (see below). The majority of experimental evidence points to an optimal latency period of 5–7 days. Theoretically, immediate distraction may prevent adequate hematoma and primordial callus generation, culminating in a regenerate of suboptimal volume/mechanical strength, and, in extreme circumstances, fibrous nonunion. It follows that disruption of initial fracture hematomas, which simulates an abbreviated latency period, results in a 26% decrease in callus cross-sectional area, and a significant impairment in the mechanical strength of the newly formed bone.³³⁷ On the other hand, deferment of the distraction period >14 days results in premature consolidation of the distraction site and device failure.^{323,329,338,339}

Overall, latency periods have been a source of debate among craniofacial surgeons and their significance held in question ever since the inception of the technique. To this end, studies comparing latency periods of 7, 14, and 21 days have

failed to underscore any difference in protocols in terms of osteogenesis.^{340,341} Clinically, Hollier and colleagues demonstrate a low complication rate with the elimination of the latency period and implementation of a rapid distraction rate (2 mm/day) in their pediatric population.³⁴² It is important to note that the nonunion rate in this series was 4.5% and was attributed to the only distracted bone graft in the study. It is generally accepted that reduced latency periods and faster distraction rates formulate an acceptable protocol in children, due to improved blood supply and osteogenic potential. A study by Slack *et al.*³⁴³ showed that children (ages 4–12) undergoing mandibular distraction demonstrate no difference in clinical outcomes up to one year postoperatively whether their distraction protocol contains a 48-hour latency period or no latency period. Flexibility in the timing and rate of distraction needs to be inherent in any successful protocol, with respect to patient profile.

Patient factors

Age

It has been well recognized that increasing age contributes negatively to the overall outcome of distraction osteogenesis, presumably secondary to limited ability of older subjects to recruit osteoprogenitor cells to the site of injury. In support of this concept, studies have demonstrated that the rate of bone formation and bone mineral deposition in pediatric distraction patients (385 mm/day) is far superior to adults (213 mm/day).³⁴⁰ This age-related difference in osteogenic potential, however, is not a contraindication to distraction osteogenesis, as older individuals can undergo surgery successfully. In this context, latency and consolidation periods may be extended to allow for protracted regenerate formation in the older patient.

Blood supply

Several studies have demonstrated that, on a molecular level, the establishment of neovascularization is critical to the formation and eventual mineralization of the regenerate. Accordingly, factors that impair vascularization of the distracted field may result in failed bone formation. Osteocyte survival depends on the proximity of less than 0.1 mm to nutrient vessels.³⁴⁴ The factors critical in osteogenesis of the axial skeleton (e.g., periosteal preservation) appear to be less important for osteogenesis in the craniofacial skeleton.^{312,323,333,337,339,345,346} There are, however, factors that unify both regions.

Radiation/chemotherapy

Radiotherapy, by compromising vascularity, cellularity, and local oxygen supply, has been known to impair osteogenesis. Limited clinical^{347–349} and animal studies^{350–353} have been performed in this regard; these studies have had mixed results. In the experimental realm, animals exposed to 36 Gy of radiation prior to the distraction process show a definitive decrease in bone mineralization microdensitometric analysis.³⁵⁴ These authors therefore propose finding an optimal radiation dosing protocol, which would make distraction osteogenesis a viable alternative in the head and neck cancer patient. Regardless of the optimal conditions for radiation delivery and in consideration of the reduced vascularity within the irradiated field,

such patients may need an extended latency period, slower distraction rate, and longer consolidation period to achieve similar outcomes in osteogenesis to the nonirradiated patient.

Many patients with malignant bone tumors will receive chemotherapy as part of their treatment plan. Chemotherapeutic agents are often cytotoxic not just to tumor cells but also to normal cells. Timing appears to be important with respect to the detrimental effects of chemotherapy on bone formed by distraction osteogenesis. Monsell and colleagues³⁵⁵ found in distracted rabbits that preoperative chemotherapy reduced regenerate bone mineral density, bone mineral content, and volumetric bone mineral density but did not alter regenerate structural integrity (i.e., the callus formed is of good quality). In contrast, perioperative chemotherapy does not alter bone mineralization but negatively impacts mechanical properties including energy at yield and yield strain.^{355,356} The latter may have clinical implications and further studies in humans are required.

Clinical application of bone transfers

Indication for bone transfers

A variety of clinical approaches are currently used to repair skeletal defects in plastic surgery. In order to provide an optimal outcome, detailed analyses of the bony defect and mechanical requirements of the reconstructed part are needed. Reconstruction of bony deficiencies can be performed using autografts (obtained from the patient), allografts (obtained from another individual), xenografts (obtained from another species), bone substitutes, or implants. The ideal is to use autologous bone grafting when possible. The type of bone graft is chosen based on the clinical scenario; medical condition of the patient; previous radiation, infection, or severe scarring of the recipient site; donor site availability; and patient and surgeon preference.

Common indications for the use of bone grafts are critical-sized bony defects from trauma, tumor resection, and congenital disease. Other indications include fracture nonunion, arthrodeses, limb-lengthening procedures, and spinal fusion. The structure and biomechanical properties of the graft determine the clinical application.

Bone graft healing and graft survival

Bone graft incorporation and fracture healing go through similar stages. Graft incorporation consists of graft resorption and replacement by vascular ingrowth and new bone (i.e., creeping substitution).³⁵⁷ Bone graft incorporation is subject to several factors: type of graft (e.g., autogenous/allogeneic, vascularized/nonvascularized), quality of transplanted bone and recipient site, mechanical properties of the graft, and systemic and local disease. The molecular and mechanical environment of the graft site, the contact between the graft and recipient bed, and the osteoinductive, osteoconductive, and osseointegrative capability of the graft influence bone graft healing.

Bone formation during remodeling is stimulated by compression, which leads to periosteal and endosteal apposition; traction, in contrast, promotes periosteal resorption and

intracortical osteolysis.³⁵⁸ Successful grafting requires a well-vascularized bed and adequate graft fixation.³⁵⁹ Mechanical stability of the healing defect allows for revascularization of the graft.³⁶⁰ Mechanical stress on a rigidly fixed graft prevents graft resorption.^{361–363} An intact periosteum also improves graft survival.³⁶¹

Cancellous versus cortical grafts

Cancellous and cortical bone grafts have different applications in skeletal reconstruction. Compared to cortical bone, cancellous bone has little immediate strength or structural support but has higher osteogenic, osteoinductive, and osteoconductive properties. It is more quickly incorporated and revascularized than cortical bone, usually within two weeks. In the transplanted cancellous bone graft, viable osteoblasts and endosteal cells line the graft surface. Cancellous bone grafts serve as an osteoconductive substrate to support creeping substitution.^{364–367} They are indicated to bridge gaps less than 6 cm in nonstress-bearing areas. Typical sources of cancellous bone grafts are iliac crest, cranial diploe, upper tibial epiphysis, and distal radius.

Cortical bone, alternatively, has limited osteogenic potential.³⁶⁸ Creeping substitution is the main mechanism of cortical bone graft incorporation, and the graft largely relies on plasmatic imbibition from the recipient bed to support the outer layer of osteocytes.³⁶⁵ The incorporation and revascularization of cortical grafts usually take one to two months.^{369–371} However, cortical grafts provide immediate structural support and are able to bridge defects up to 12 cm. Cortical grafts should be tailored to the defect. Generally, rigid fixation is required to prevent fracture of the healing graft.³⁷² Cortical grafts are often used for onlay augmentation of contour deficits. Typical graft sites include fibula, rib, and iliac crest.

Clinical considerations

To optimize the chance of survival, the bone graft should be handled as follows³⁷³:

1. Graft exposure time to air at room temperature should be minimized (ideally to less than one hour to maintain cell viability).³⁷⁴ However, longer periods of ischemia can be tolerated by bone cells if the medullary nutrient blood supply is later reconstituted, as in vascularized bone.³⁷⁵
2. To enhance bone viability by four to six hours, a graft should be covered in a blood-soaked sponge with a moist saline gauze on top. If longer periods of graft exposure are required, cell viability can be maintained if the graft is stored in 10% human serum albumin and a 90% balanced salt solution at 3°C in Collins–Terasaki solution.³⁷⁵
3. Grafts should be kept cool, as temperatures over 42°C may cause cell death.
4. Antibiotic washes are not only bactericidal but are also cellucidal and therefore should be used with caution.
5. Dead space around the graft should be avoided.
6. The cancellous portion of the graft should be placed in contact with the cancellous bone in the bed.
7. Ideally, the graft should be placed in a previously prepared vascularized bed to increase graft survival.

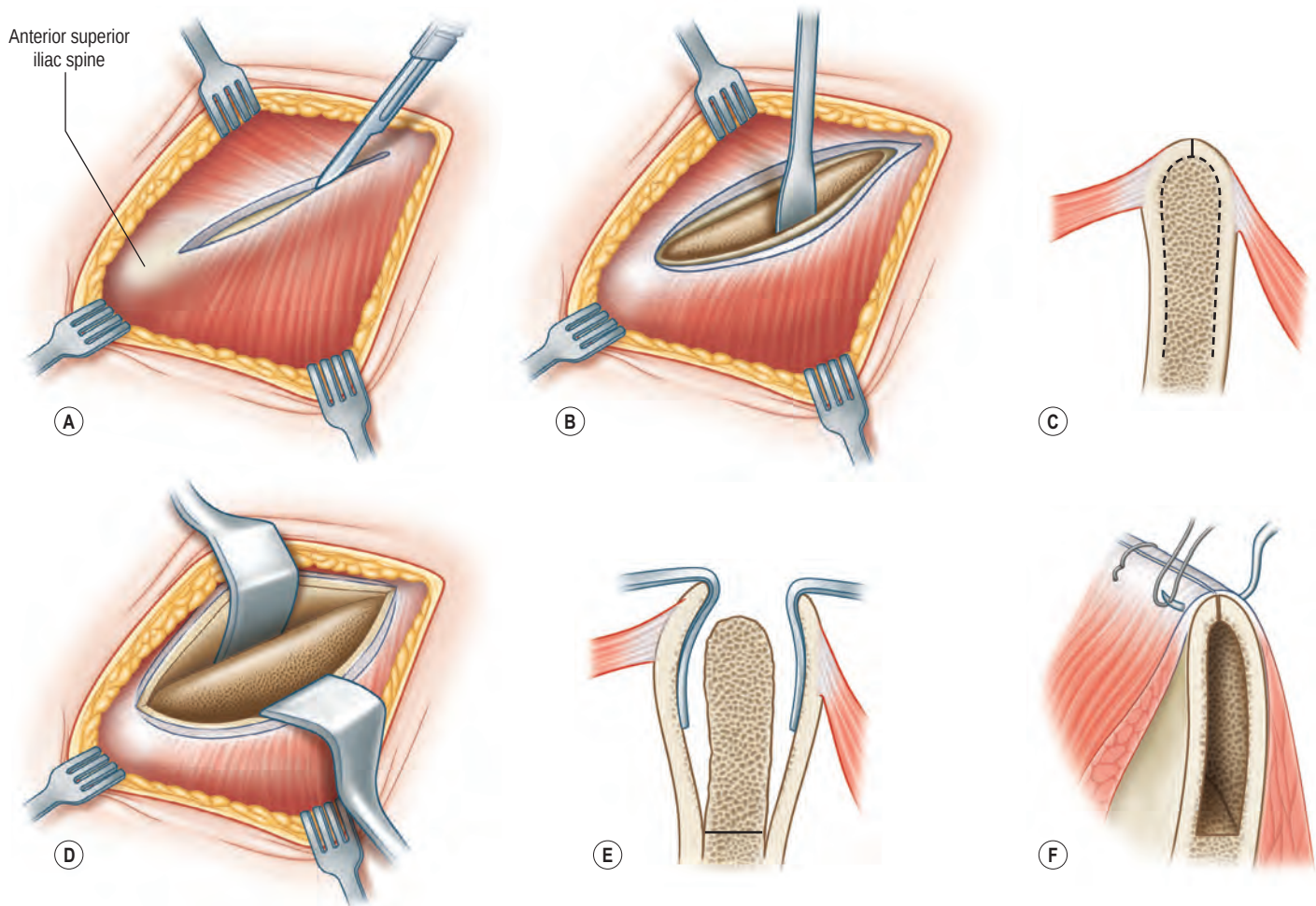


Fig. 18.9 A technique for removal of cancellous bone from the ilium. **(A)** Incision of the periosteum after exposure of the crest. **(B)** Separation of the cortex with an osteotome. **(C)** Cross-section showing lines of separation of the inner and outer cortex from the cancellous bone. **(D)** Exposure of cancellous bone. **(E)** Cross-section showing exposure. **(F)** Reunion of the inner and outer cortex by stainless steel wire suture. ((A–F) From Cutting CB, McCarthy JG, Knize DM. *Repair and grafting of bone*. In: McCarthy JG (ed). *Plastic Surgery*. Vol 1. Elsevier; 1990. (F) After Tessier P, Kawamoto H, Matthews D, et al. Taking bone grafts from the anterior and posterior ilium – tools and techniques: a 6800-case experience in maxillofacial and craniofacial surgery. *Plast Reconstr Surg*. 2005;116(Suppl):25S–37S; see also Wolfe SA, Kawamoto HK. Taking the iliac-bone graft. *J Bone Joint Surg Am*. 1978;60:411.)

Techniques of harvest: autologous bone grafts

Ilium

The ilium is the most commonly used site for corticocancellous bone grafts (Figs. 18.9, 18.10). The clinical indications are wide due to the versatility of the ilium, the large amount of cortical and cancellous bone available, and the possibility to transfer it as a vascularized bone flap. The iliac crest is easily accessible and has limited morbidity if proper technique is employed. Complications include chronic donor site pain, paresthesias, and gait abnormalities.³⁷⁶

The harvest technique should preserve the shape of the iliac crest by careful and proper splitting. Correct handling of the iliac wing permits its regeneration and allows for further or repeat harvest. Additionally, wiring the split iliac crest back together can decrease postoperative pain. Care must be taken to avoid stretching the lateral femoral cutaneous nerve by unnecessary superior dissection, to avoid tearing the gluteal muscles, and to avoid removing the iliac crest itself.

Preservation of the insertion of the abdominal and gluteal muscles on the iliac crest is key. Dependent upon the amount of graft taken, the outer, inner, or both cortical plates of the iliac wing need to be preserved. The amount of cancellous bone that can be harvested from the ilium is quite large – down to the cotyloid ridge above the glenoid fossa. A large subcrest corticocancellous graft up to 11 cm, a 6×10 cm corticocancellous inner plate, and an approximately 5×8 cm corticocancellous outer plate can also be harvested. Harvest of the anterior iliac crest (see Fig. 18.9) is convenient due to supine patient position. However, the posterior iliac crest provides a larger amount of graft and avoids aberrant entry into the abdomen. To prevent avulsion fractures of the anterior superior iliac spine (ASIS), the anterior approach should stop 3 cm posterior to the ASIS. The posterior approach should stop 4 cm anterior to the posterior superior iliac spine to prevent injury to the sacroiliac joint.³⁶⁸

The anterior approach can be performed in supine position or with a roll underneath the patient's hip to raise it. The following landmarks are drawn: ASIS and the tubercle of the iliac crest. The incision is placed over the iliac crest and is

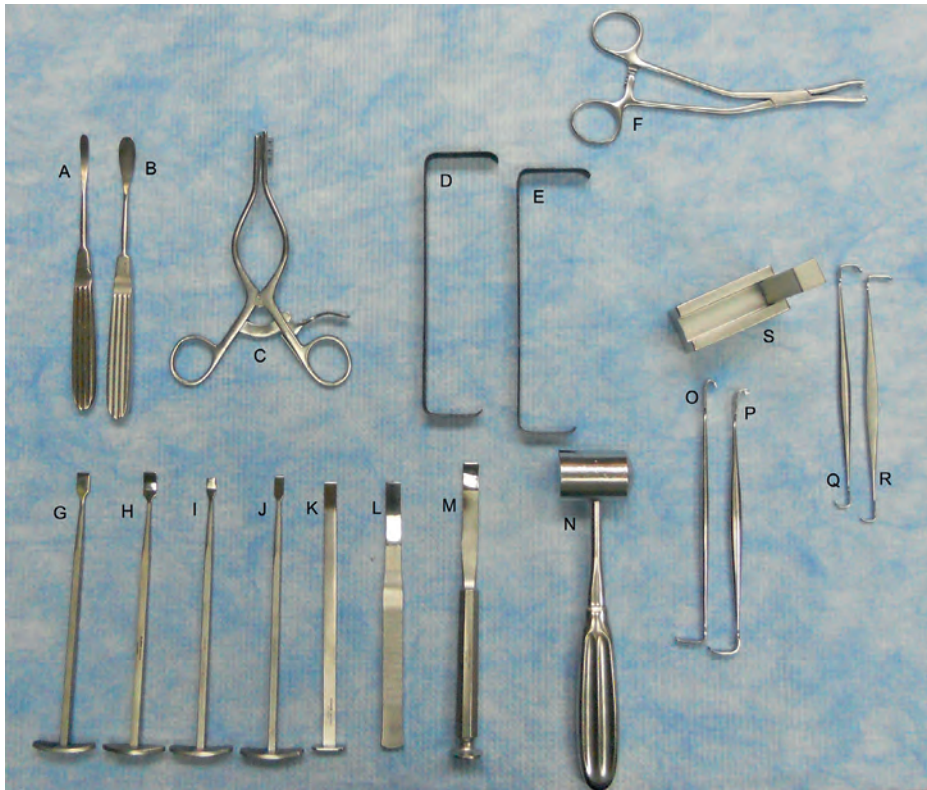


Fig. 18.10 Instruments for ilium harvest.
 (A) Obwegeser periosteal elevator, 6 mm.
 (B) Obwegeser periosteal elevator, 12 mm.
 (C) Wheatlander retractor. (D, E) Farabeuf retractors.
 (F) Digman bone-holding forceps. (G–M) Osteotomes,
 4–12 mm, straight and curved. (N) Mallet.
 (O, P) Senn retractors. (Q, R) Ragnel retractors.
 (S) Cottle crusher.

6–10 cm in length. By pulling the skin medially, the incision actually resides 3–5 cm below and lateral to the iliac crest. No subcutaneous dissection is necessary; the abdominal soft tissue is retracted medially and the crest, tuberosity, and anterior spine are palpated. A cartilaginous cap is frequently encountered overlying the bone and this must be split to access the cortical plate. The next step is to split the iliac crest; the split is extended just behind the anterior spine. The medial leaf of the split crest is created and moved medially as a single piece with the attachments of the abdominal muscles. The same maneuver is performed for the lateral leaf with attention to the convexity of the lateral crest. The grafts are extracted according to defect size and shape.³⁷⁷ Excessive retraction can potentially cause injury to the lateral femoral cutaneous nerve, which travels retroperitoneal on the deep surface of the iliac muscle, down to the inguinal ligament near the ASIS. This can result in postoperative paresthesias.

Prior to closure, hemostasis is achieved using electrocautery or bone wax (e.g., bleeding from the central artery of the iliac bone).

Gelfoam can be placed in the periosteal pocket, and the iliac leafs are wired back together. Muscles, subcutaneous tissue, and skin are closed in a layered fashion over a suction drain. A pain pump catheter delivering local anesthetics can be inserted in the wound for better postoperative pain control.³⁷⁸ In similar fashion, the posterior iliac crest can be harvested from the supine or prone position. When harvesting this region of the crest in the prone position, one must take care to avoid injury to the cluneal nerves.³⁷⁸ Also, in order to prevent injury to the sacroiliac joint, the most posterior mark with the osteotome is made 4 cm anterior to the posterior iliac spine.³⁶⁸

Complications are rare if proper technique is used, as shown in a summary of 5600 patients with a resultant complication rate of 0.5%.³⁷⁷

Tibia and fibula

The tibia was mainly used as a source of corticocancellous bone graft during World War I and II. Its use has decreased in popularity due to donor site morbidity and pathologic fractures. The tibia remains a favorable donor site in various centers in Scandinavia and the UK when only small amounts of cancellous bone are needed (e.g., alveolar bone grafting).^{379,380} A detailed description of technical aspects of tibial harvest has been given (Fig. 18.11).³⁸¹

The use of fibula grafts has decreased with the availability of allograft. Currently, the fibula is mainly used as a vascularized transfer for mandible reconstruction, as well as midface and extremity reconstruction.

Greater trochanter and olecranon

The greater trochanter and the olecranon are potential sites of cancellous bone harvest, specifically when small amounts are needed. The harvest technique is similar to a bone biopsy. A small incision is made overlying the area of interest, dissection is carried down to the bone, and the periosteum is removed from the desired area. An osteotome can be used to transect the cortex or a small drill bit can be used to create perforations in an elliptical pattern, which then can be connected with an osteotome. Through this opening, cancellous bone can then be harvested with a curette. After completion of the harvest, the cortical bone piece can be reinserted, or if need be, can be used as part of the graft. Hemostasis is achieved using gelfoam and

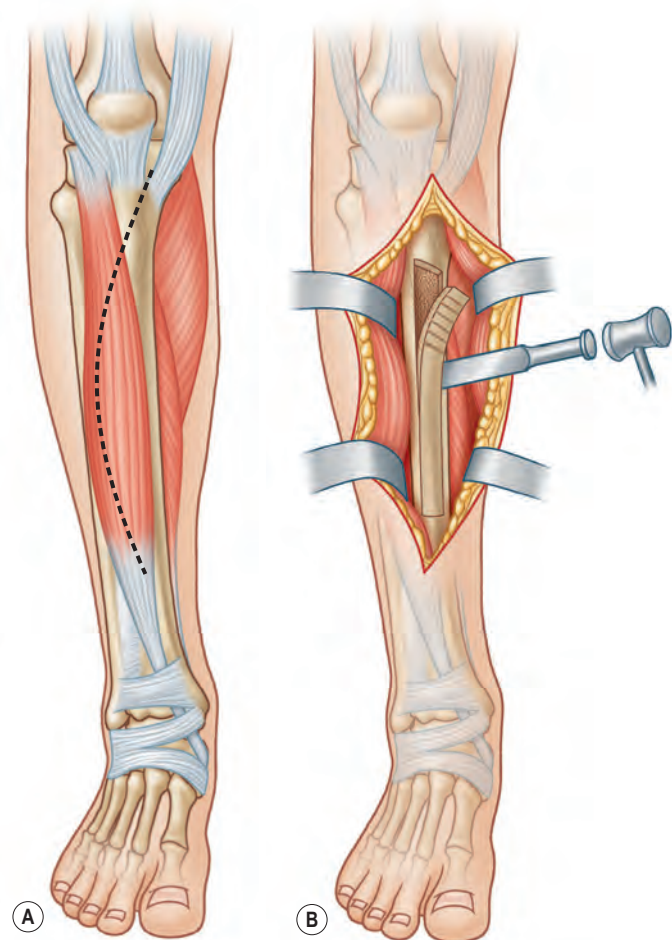


Fig. 18.11 Tibial bone grafts. (A) Incision for removal of the graft. (B) Removal of the graft with an osteotome.

thrombin. A layered closure is performed and a compression dressing applied.³⁷⁶

Rib

Rib can be used as graft or as a vascularized transfer. Rib grafts are flexible, which allows for easy bending and wire fixation. Also, rib integrates well to recipient bone. However, ribs are fragile and do not allow for stable screw fixation. Furthermore, the amount of cancellous bone is minimal and a second harvest is implausible due to poorly regenerated rib.

When harvesting rib, short skin incisions should be used and one rib should be skipped to preserve contour and stability of the thoracic wall (Figs. 18.12, 18.13). If possible, the surgeon should avoid subcutaneous dissection and transection of the rectus muscle. Also, one must be cognizant of bleeding from the intercostal vessels as well as air leaks. The harvest can be performed with the patient in the supine or lateral position. The skin incision should be located over the rib that is to be harvested or over the skipped rib if two ribs are required. Dissection is carried down to the rib, and the periosteum is incised longitudinally on the lateral aspect of the rib. Subperiosteal elevation should then be performed up to the costochondral junction. The length of the rib to be harvested is determined

based on the amount needed: a long segment from one rib is preferred over a short segment from two ribs. If cartilage is needed, it can be included in the harvest.

After harvest, the wound should be irrigated and examined for an air leak and then closed in a layered fashion. This takes place by suturing the edges of the periosteum and performing a layered closure of the muscles, subcutaneous tissue, and skin. A suction drain and local pain pump can be added if the surgeon desires.

The associated donor site morbidities and risks include pneumothorax, which can easily be prevented if careful and proper technique is used. In addition, the chest wall might become deformed if consecutive ribs are harvested. Postoperative breathing difficulties secondary to pain can affect postoperative recovery time. Overall the complication rate is low but varies within the literature. Complications may include pain, intraoperative bleeding and air leaks, secondary bleeding, and rarely, chest wall deformities or scoliosis.³⁸²

Calvarium

Calvarial grafts are ectomesenchymal, with a rich diploic vascular system that allows for rapid revascularization of the haversian systems. This facilitates osteocyte survival, leading to less resorption and increased structural maintenance.³⁸³ Calvarial grafts are ideal candidates for calvarial, midfacial, nasal, and orbital reconstruction.³⁸⁴ They are obtained as split- or full-thickness grafts. In young children, however, a split graft may not be feasible because of a thin calvarium. Harvest can occur via *in situ* splitting of the outer table or full-thickness harvest and on-the-table splitting to increase the surface area of graft available.³⁸⁵ It is important to use correct instruments

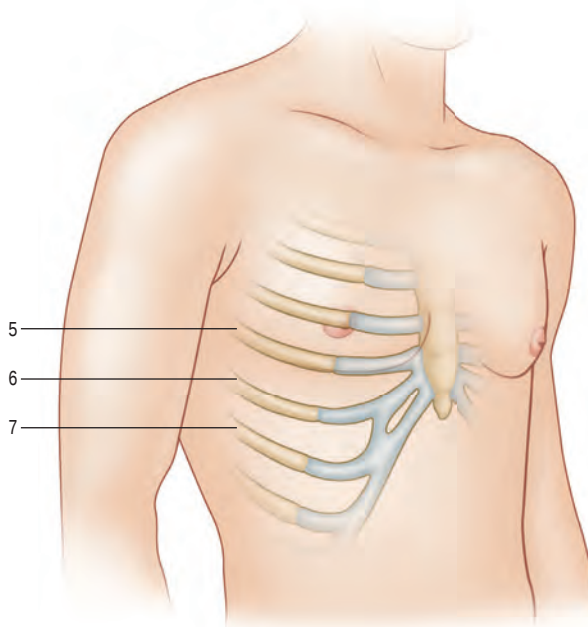


Fig. 18.12 Ribs 5–7 are the most commonly used donor ribs. (From Tessier P, Kawamoto H, Matthews D, et al. Taking long rib grafts for facial reconstruction – tools and techniques: III. A 2900-case experience in maxillofacial and craniofacial surgery. *Plast Reconstr Surg.* 2005;116:385.)



Fig. 18.13 Instruments for rib harvest. **(A)** Bone-cutting forceps. **(B)** Stille-Listor angled bone-cutting forceps. **(C)** Alexander-Farabeuf periosteotome. **(D, E)** Doyen elevators. **(F)** Frykholm bone rongeur. **(G)** Rib shears. **(H)** Tessier bone bender.

that are functional (Fig. 18.14). The surgeon must be aware of the location of the sagittal and coronal sutures, as the corticotomy should not occur less than 1 cm from the coronal suture or less than 1.5 cm from the sagittal suture. It is additionally important to locate the perforating vessel posteriorly near the sagittal suture.

The technique of calvarial bone graft harvest includes a coronal incision that is made through scalp and galea. The pericranium is then incised and elevated. Bone wax and/or gelfoam can be used to halt bone bleeding. The landmarks include the coronal suture, the sagittal suture (with its posterior perforating vessels), the anterior temporal crest, and the



Fig. 18.14 Instruments for calvarial harvest. **(A)** Obwegeser periosteal elevator, 6 mm. **(B)** Obwegeser periosteal elevator, 12 mm. **(C, D)** Farabeuf retractors. **(E)** Tessier bone bender. **(F)** Digman bone-holding forceps. **(G-K)** Dautry-Munro osteotomes, straight and curved. **(L)** Straight osteotome. **(M)** Stille osteotome, 15 mm. **(N)** Mallet.

intraosseous lateral vein. When taking a split *in situ* outer-table graft, the design can be outlined and traced with an oscillating saw followed by burring until diploe is seen. The alternating straight and curved osteotomes are used to split the calvarium. After the splitting of the outer table, further strips of diploe can be harvested until the inner table is encountered specifically at the thicker, posterior border near the lambdoid suture. If during this process the dura becomes exposed, it can be covered with bone chips. The pericranium can be closed over Surgicel® and the scalp should be closed in layers over suction drains.

There are several factors that make an intracranial approach for calvarial bone graft harvest a better option. Specifically, an intracranial approach should be undertaken in children with a thin calvarium, when a large graft is needed, in a patient with an irregular skull shape, or if, for graft design purposes, the inner table is more feasible. Availability of a neurosurgeon is recommended for this approach. Once the full-thickness piece is obtained, it can be split on the back table. One should not use a saw but rather an osteotome to reduce the waste of bony substance and to reduce heat damage to the graft. It is important to make sure that no cerebrospinal fluid leak is present and that hemostasis is achieved. One split segment is returned to the donor site; the other is used for reconstruction.

Overall, complications are rare (0.25%). Intraoperative incidents such as bone bleeding, dural bleeding, and dural laceration are usually controlled during surgery. Postoperative complications include minimal pain and occasional paresthesia, subscalp hematoma and calvarial irregularities, infection, and rare brain injury with transient neurological sequelae.³⁸⁶

Vascularized bone flaps

Vascularized bone flaps avert the reparative phase of nonvascularized grafts and do not depend on recipient bed vascularity. Specifically in circumstances of prior radiation, extensive trauma, or chronic scarring, vascularized bone flaps are superior to nonvascularized bone grafts.^{387–390} The survival of osteocytes in vascularized bone flaps leads to a decrease in the remodeling process during revascularization as well as the maintenance of bone mass and strength.^{391–394} Other advantages include increased blood flow to compromised recipient sites; utilization of composite tissue flaps, including skin, muscle, and nerves; and the growth potential when including a growth plate in the flap.^{395–400} An important indication for the use of vascularized bone flaps is segmental defects of greater than 6–8 cm after traumatic or oncologic bone loss; composite tissue loss; bony nonunion; avascular necrosis; osteomyelitis; or biologic failure.^{401–404}

Vascularized iliac transfer

The ilium, also a great source of graft material, has a robust periosteal blood supply in addition to the nutrient artery. Many studies have evaluated the best blood supply to the ilium.^{405,406} The superficial circumflex iliac vessels are often utilized in conjunction with a groin fasciocutaneous flap, but the deep circumflex iliac vessels offer a better blood supply to the bone (Fig. 18.15). Furthermore, a piece of vascularized iliac crest can be harvested in conjunction with the anterolateral thigh flap based off the lateral femoral circumflex system, with the ascending branch giving a small vascular pedicle to

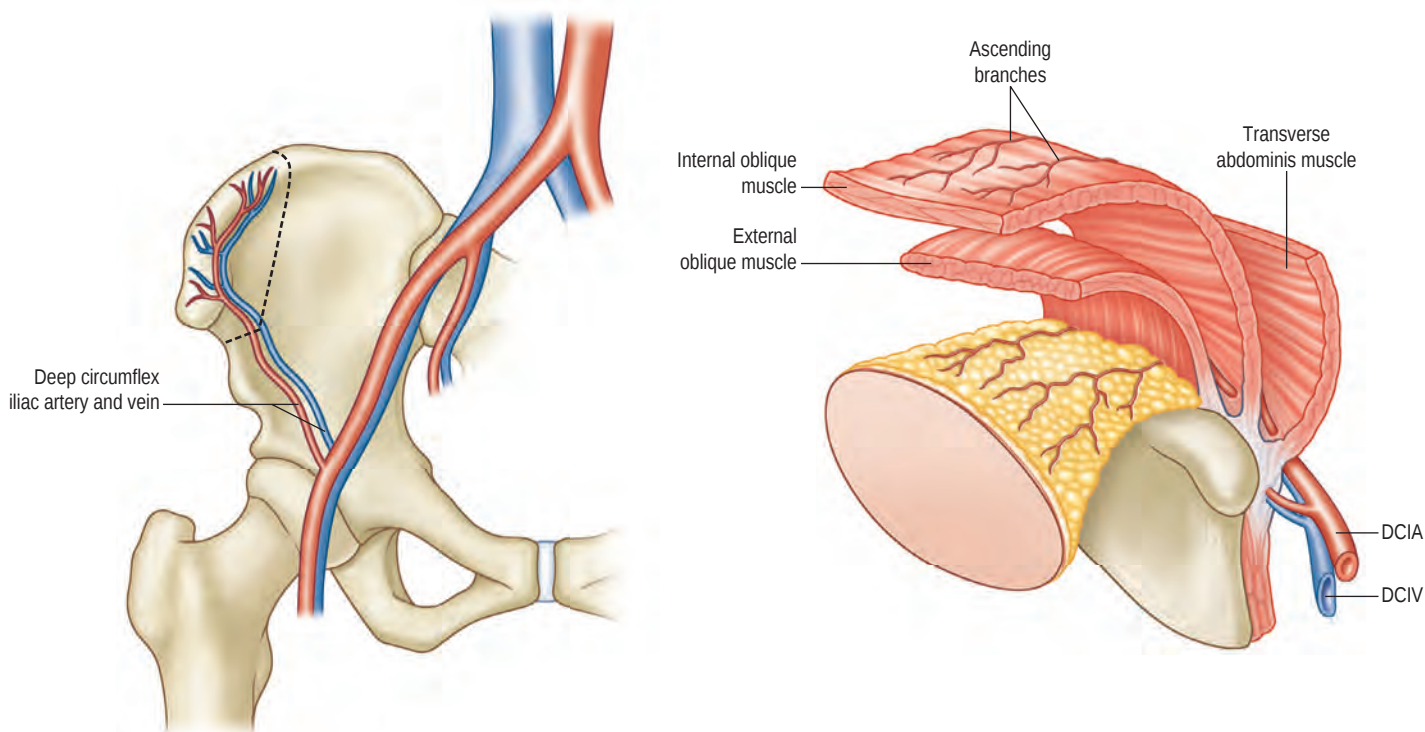


Fig. 18.15 The deep circumflex artery vascularized bone flap. Vascularized bone based on the deep circumflex iliac artery and vein (DCIA/DCIV) is harvested and can be taken with an overlying skin paddle.

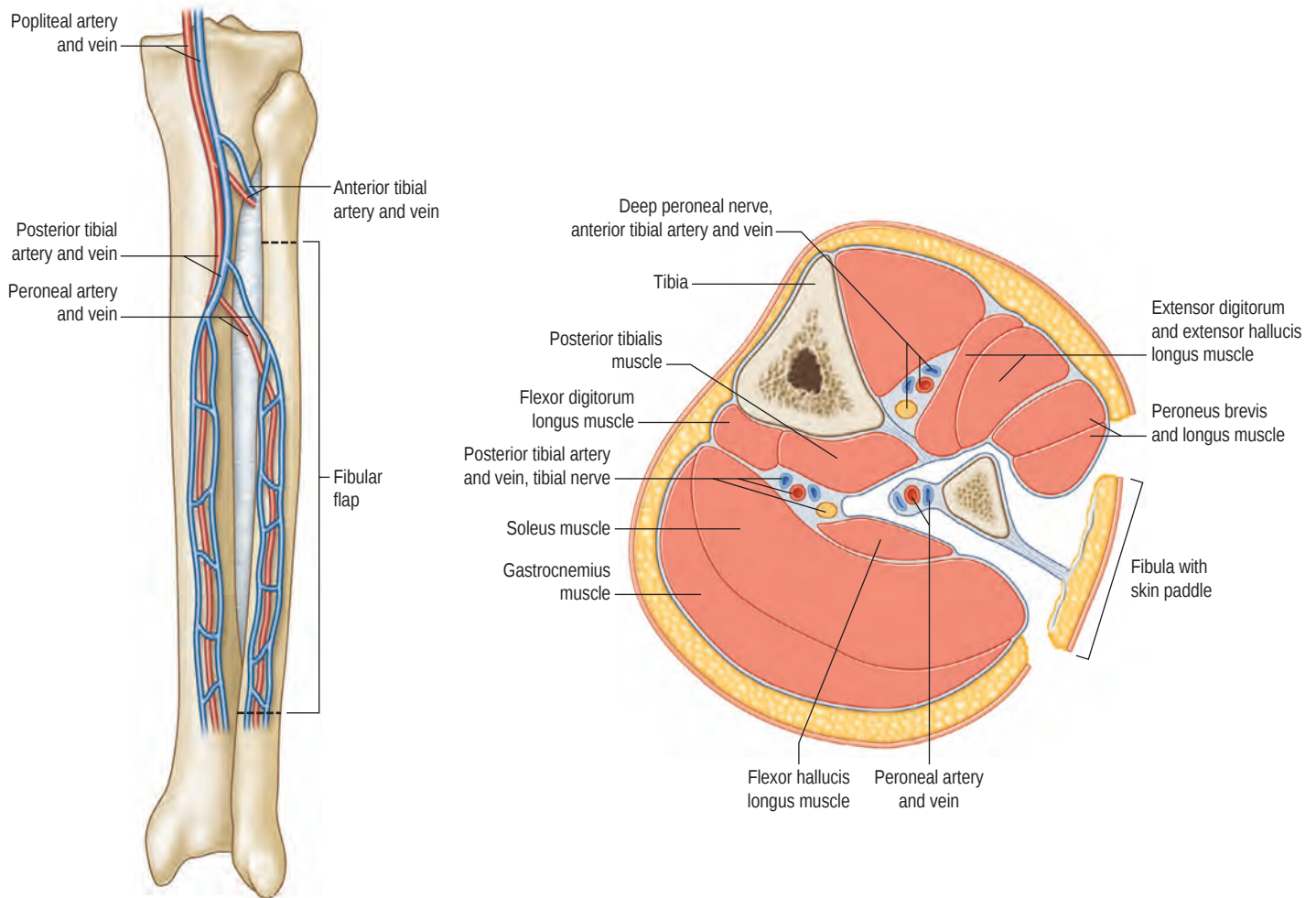


Fig. 18.16 The fibula free flap. Vascularized fibula is based on the peroneal artery and vein pedicle and can be raised with or without an overlying skin paddle.

the anterior superior iliac crest.^{407,408} Details of vascularized bone transfers can be found elsewhere in this series.

Vascularized fibula

The free fibula transfer is utilized mainly in mandibular and occasionally in midface reconstruction as well as for long-bone defects or nonunions. The fibula provides a straight piece of cortical bone up to 30 cm. The principal blood supply is via the nutrient artery, a branch of the peroneal artery with a diameter of 1.5–3 mm (Fig. 18.16). The fibula is also supplied by periosteal branches from the peroneal artery proximal to the nutrient vessel and musculoperiosteal branches distally. Dissection is performed through an anterior or posterior approach and bone can be transferred with adjacent muscles (e.g., soleus, peroneal, flexor hallucis longus). Fasciocutaneous perforators supply a skin paddle up to 10×20 cm.⁴⁰⁹ Though the surgical steps are described elsewhere, it is important to leave 6 cm of fibula distally to maintain a stable ankle joint. Also, rigid fixation of the transferred bone at the recipient site will improve healing. Complications include instability of the ankle joint, persistent pain, neurological compromise, and wound breakdown. A skin graft may be required if a skin paddle was included. Various series have shown significant complication rates, approaching 20% to 50%.^{410,411}

A unique advantage of free vascularized fibula transfer is the ability to include the physis within the flap based on the anterior tibial artery and vein.⁴¹² This is particularly useful in children with a malignant bone tumor located in an area that requires extirpation of all or part of a long bone including the native growth plate.

Vascularized scapula

The vascularized scapular bone flap can be combined with a variety of possible composite flaps that include varying amounts of muscle and skin. The scapula can be transferred as vascularized bone based on the nutrient artery, which enters inferior to the lateral attachments of the acromion to the scapula plate. Chimeric free flaps containing vascularized scapula, as well as rib and/or iliac crest, are particularly useful for “hostile” defects, composite defects in the setting of cigarette smoking, radiation, or scarring.^{413,414}

The scapula bone flap can be harvested off the lateral scapular border based on the circumflex scapular circulation or off the medial scapular ridge also based on the circumflex scapular circulation as well as on periosteal blood supply.^{415–417} The scapular bone can also be based on the angular branch of the thoracodorsal system, which supplies the scapular wing.⁴¹⁸ The mean pedicle length of the circumflex scapular system is

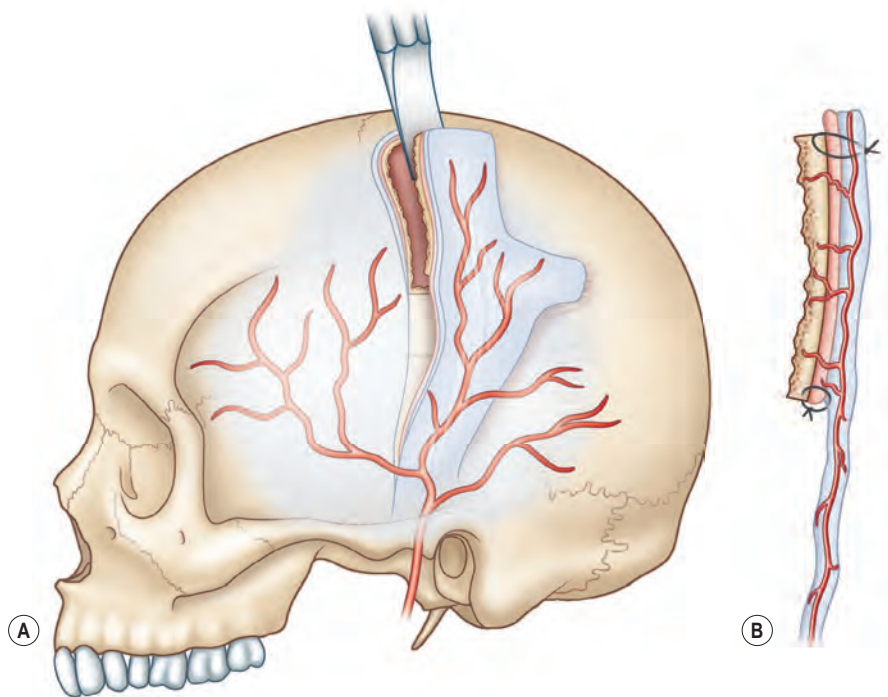


Fig. 18.17 (A) The outer table of the parietal bone is harvested with a curved osteotome after a trough is created around the periphery of the bone flap. The blood supply of the bone flap is maintained by preserving the periosteal blood vessels in continuity with the superficial temporal artery system within the galea superficial musculoaponeurotic system and the deep temporal fascia. (B) Sutures passed between the overlying galea, periosteum, and calvaria are helpful in keeping the periosteum attached to the bone and preserving the blood supply.

7.5 cm. It can, however, be increased up to 13–15 cm by clipping the circumflex scapula perforators, which allows the bone to be supplied by the angular vessels, thus avoiding the need for vein grafts.⁴¹⁹

During flap dissection the teres major and minor muscles need to be divided, which can cause shoulder dysfunction. Another potential complication is scapular winging from division of serratus anterior. Vascularized scapular bone might offer an advantage over fibula or iliac crest in older patients in whom ambulation is essential for postoperative recovery.⁴²⁰

Vascularized rib

The rib provides a curved, malleable piece of bone up to 30 cm long that receives its vascular supply through nutrient and periosteal vessels. The nutrient vessel arises from the posterior intercostal vessels and the periosteal blood supply from various nearby sources (intercostal, internal mammary, lateral thoracic, and thoracoacromial). The overlying muscle, skin, and fat of each region can be transferred with the flap.⁴²¹ A composite flap can be particularly helpful for reconstruction of complex three-dimensional (3D) cranial defects.^{422,423} A dissection that includes the nutrient vessel within the flap requires thoracotomy, adding difficulty and associated risks. Therefore, most vascularized rib transfers are based only on the periosteal blood supply.

Vascularized calvarium

The vascularized calvarial flap is useful for unfavorable recipient sites (irradiated or scarred) as well as in midface reconstruction.⁴²⁴ An understanding of the anatomy of the temporoparietal region is important to utilize this area for reconstructions with vascularized bone. Calvarial bone is covered with pericranium, overlying temporal muscle,

temporal fascia (deep and superficial layers), subgaleal fascia, superficial temporal (temporoparietal) fascia, subcutaneous tissue, and skin. Different flap types based off the superficial and deep temporal system can be useful to reconstruct midface and other facial defects.⁴²⁴

A temporoparietal fascial flap can be harvested with parietal bone vascularized by periosteal vessels from perforators of the superficial temporal system (Fig. 18.17). A vascularized calvarial flap can also be harvested with a fused segment of the deep and superficial temporal fascial flap 2 cm above the orbital rim.³⁸⁵ This flap is based on the middle temporal artery. A third option is a temporalis myo-osseous flap, which transfers the temporalis muscle and distal periosteum with the underlying bone as one unit. This is based off the deep temporal vessels.⁴²⁵ The parietal bone can be harvested as a partial (outer table) or full-thickness flap while avoiding the sagittal sinus (Fig. 18.18).

The surgical steps include a preauricular incision extending into the hairline, the elevation of flaps and dissection down to temporoparietal fascia, and a decision of flap level elevation and flap harvest with the appropriate pedicle, as described above. The pedicle is dissected into the pericranium of the desired calvarial bone. The bone flap design is based on the defect and reconstructive needs of the patient. Multiple strips can be harvested for complex three-dimensional defects. Stable fixation of the cranial bone flap at the recipient site is essential for reliable early bone integration.

Principles of bone transfer

Principles of bone grafting must be understood to optimize outcomes. Knowledge of these principles arises from three components: individual experience, experience of others (literature review), and knowledge acquired from basic science research.⁴²⁶ There are general principles and specific

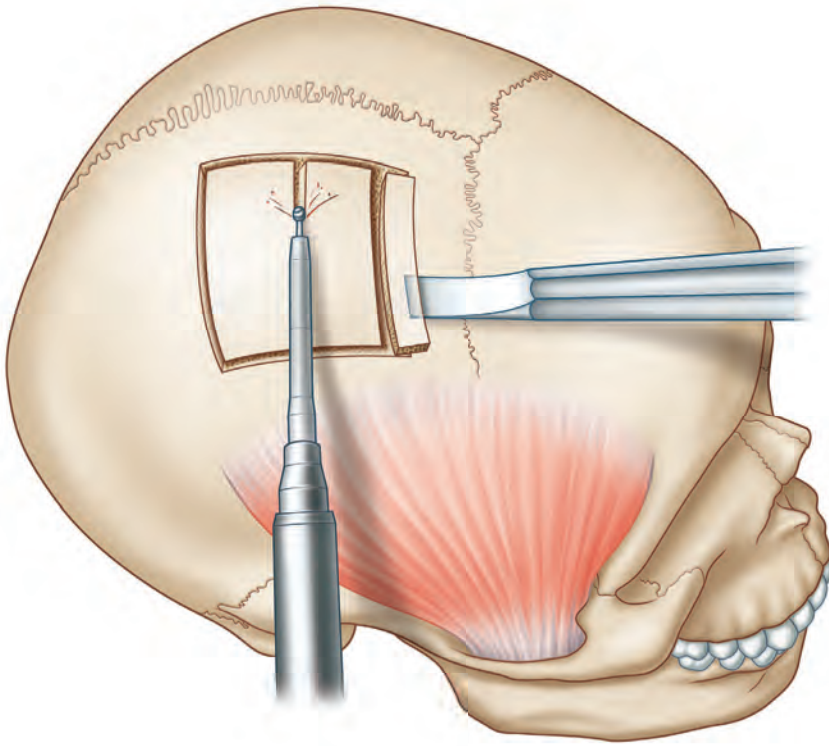


Fig. 18.18 The parietal bone donor site. (From Tessier P, Kawamoto H, Posnick J, et al. Taking calvarial grafts, either split in situ or splitting of the parietal bone flap ex vivo – tools and techniques: V. A 9650-case experience in craniofacial and maxillofacial surgery. *Plast Reconstr Surg*. 2005;116:55S.)

doctrines. The general principles include defining goals and priorities; taking into consideration the location, size, depth, and etiology of the defect; the quality of the surrounding tissue; presence or history of infection; pre- or postoperative irradiation; age and health of the patient; status of disease (control or palliation); and functional and appearance-related considerations.⁴²⁷ The specific doctrines include the harvesting of bone from areas with which one is familiar, contouring of the bone graft to fit the defect, fixing the bone graft in a tension-free manner, ensuring absolute graft immobilization, differentiating between child and adult grafts, avoiding contaminated sites, proper handling of the graft, ensuring adequate blood supply over the graft, and assessing graft take periodically.⁴²⁶

If the recipient site is compromised due to scarring, infection, or irradiation, or if greater biomechanical strength is required for segmental defects greater than 6 cm in a load-bearing area, a vascularized bone transfer should be considered. The maintained/re-established vascular supply to the transferred bone leads to rapid healing with less resorption and greater biomechanical strength.^{392,393}

Allogeneic bone grafts

A bone allograft is harvested from a genetically dissimilar individual of the same species. The use of allogeneic bone for reconstruction of large bony defects in the axial and peripheral skeleton has grown in the last decade due to improved methods for bone preservation and sterilization. Nonvascularized bone allografts are free of any viable donor cells after antigen extraction and autolysis. These acellular constructs therefore mainly act as a scaffold for ingrowth of recipient mesenchymal cells, which repopulate the donor

by creeping substitution. Advantages over autogenous bone grafts include an unlimited supply, a lack of donor site morbidity, and decreased operative time. Disadvantages include the lack of osteogenic properties in prepared allografts as well as the immunologic response of fresh bone allografts. Due to slow union, long-term fixation is required.

Although allogeneic bone is a reasonable option in cases of insufficient autogenous bone or when only very limited allogeneic bone is needed for reconstruction, autogenous reconstruction leads to better graft incorporation and outcomes.⁴²⁸ Allogeneic bone grafts can also be combined with autogenous grafts for defect repair.⁴²⁹ These hybrid grafts offer the pro-osteogenic properties of autogenous bone while minimizing the main drawbacks.

Processing and preservation

Allografts can stimulate the host immune system and therefore are prepared by removing all viable cellular components in order to minimize this immune response. The goal is to create a sterile, acellular, biocompatible, and osteoconductive product. During preparation and preservation within tissue banks, the allograft loses its osteogenic and osteoinductive properties.

Processing techniques include mechanical debridement, ultrasonic or pulsatile water washes, ethanol washes, antibiotic soaks, and terminal sterilization with moderate-dose (<20 kGy) irradiation. Larger doses (>30 kGy) are needed to neutralize significant viral loads, but will weaken the bone significantly.⁴³⁰ The preservation of allografts can be achieved with deep-freezing (−70°C) or freeze-drying. Freeze-drying may cause a larger decrease in bone strength compared to deep-freezing.⁴³¹

Risk of disease transmission

The risk of disease transmission from processed allografts is minimal due to extensive donor screening and testing as well as the acellular nature of the graft.^{432,433} The pathogens of main concern are human immunodeficiency virus (HIV), hepatitis B virus (HBV), and HCV. Using donor screening recommendations, the transmission risk for HIV is estimated to be one in 1.67 million.⁴³³ However, this risk is probably lower with current screening and processing techniques.

Immunogenicity

Host immune reactions caused by allografts depend upon the degree of antigen mismatch between donor and host and the process of graft preparation. The immune system responds to fresh allografts via humoral and cell-mediated mechanisms; fresh frozen allografts, however, predominantly activate the cell-mediated immune system. The cell-mediated response is due to mismatch among cell surface major histocompatibility class (MHC) I and II antigens. Interestingly, freeze-dried allografts elicit only a minimal immune response.⁴³⁴ Signs of graft rejection, which are not as apparent as in solid organ rejection, include resorption and mechanical dysfunction. Chronic rejection may cause impaired allograft remodeling due to the sequestration of the implant in a fibrous capsule. The rejection process can be diminished by cyclosporine administration.⁴³⁵

Incorporation of allograft bone

The phases of allograft incorporation are similar to fracture repair. They include an initial limited inflammatory response with increased vascularity, followed by resorption, bone formation and remodeling. Cancellous bone is incorporated quicker than cortical grafts. The biomechanical strength of allografts after incorporation is lower than that of autografts, and this needs to be taken into consideration when reconstructing weight-bearing bones.

Formulations of allogeneic bone grafts

There are several formulations of allograft bone available including DBM, morselized cancellous chips, cortical and corticocancellous grafts, and whole bone segments. Demineralized bone preparations are not osteogenic, but they are osteoinductive and provide scaffolding upon which new bone can be formed.^{436–438}

Xenogeneic bone grafts

Xenografts are taken from a genetically different species. They undergo a high rate of resorption, and their immunogenicity, specifically due to matrix and serum proteins, limits their clinical utility. Deproteinized and defatted xenograft preparations demonstrate decreased immune stimulation but also demonstrate destruction of BMPs and other growth factors. Xenogeneic grafts are clearly inferior to autografts and allografts.⁴³⁹

Bone substitutes

Alloplastic cranioplasty is a concept as old as trephination. From the Incan use of precious metals, to the first documented use of a synthetic material to repair a cranial defect (Fallopian,

16th century), to Meekeren's use of canine bone in a human subject, the quest for a suitable nonautologous material has been ever present.⁴⁴⁰ The ideal bone substitute has the following characteristics: (1) chemically inert; (2) hypoallergenic or incapable of inducing a foreign-body reaction; (3) easily contoured; (4) stable and durable shape retention; (5) noncarcinogenic; and (6) capable of incorporation into or replacement with living tissue from the recipient. Although this ideal has not been achieved, several products are available and are discussed below. The following discussion is based upon the three broad categories of substitutes used in clinical practice: (1) cement pastes; (2) biomaterials replaced by bone; and (3) prefabricated polymers. Finally, we discuss scaffold biomimicry used for the engineering of osseous tissue.

Cement pastes

Calcium phosphates

Resembling the inorganic form of bone, hydroxyapatite and related composites have been available for FDA-approved clinical use since 1994. Calcium phosphate substitutes have supplanted calcium sulfate variants due to their closer resemblance to bone, higher biocompatibility, and tendency to undergo less resorption. Two main forms are available for use: ceramic pastes and cement pastes. Ceramic hydroxyapatite constructs (e.g., Interpore, Interpore International, Irvine, CA), although difficult to mold, demonstrate less resorption and better osteoconduction than their cement counterparts, as demonstrated in a series of animal experimentation.³⁰⁰ These authors were able to demonstrate that the higher the pore size, the greater degree of osteoconduction and osteoinduction, as substitutes composed of pure ceramic hydroxyapatite, or cement forms of higher TCP (80% TCP/20% hydroxyapatite) exhibited greater replacement by lamellar bone histologically.³⁰⁰ The latter formulation was osteoinductive by virtue of the relatively high TCP content that yields to resorption and replacement by macropores. The cement form of this material has been quite popular, due to its biocompatibility, malleability, and relative ease of handling. Due to the limited scope of this chapter in this regard, only two major commercially available forms of bone cement will be discussed: BoneSource and Norian. The reader interested in further review is directed elsewhere.^{441,442}

BoneSource

The first commercially available calcium phosphate cement,⁴⁴³ BoneSource (Stryker Leibinger, Inc.) is based on a mixture of tetracalcium phosphate and dicalcium phosphate dehydrate and activated with water at a 4:1 ratio prior to use. After an isothermic reaction, the resulting paste can be contoured on the field, setting into pure hydroxyapatite within 20–25 minutes. Final set time is 4–6 hours.⁴⁴⁴ A dry operative field is mandatory for this biomaterial to reach its final cured state. In this state, BoneSource achieves a compressive strength of 50 MPa and a diametral strength of 8 MPa.

BoneSource has been used over the years in numerous applications on the craniofacial skeleton. Providing one of the largest series to date, Burstein and colleagues⁴⁴⁵ reviewed their experience with this product in 61 patients

retrospectively (20-month mean follow-up). Inlay and onlay grafting were performed over a 3-year period. Postoperative complications were present in 11% of patients, mainly seromas. Interestingly, the authors used slow-release antibiotic therapy (1 g cephalosporin mixed with 10 g of cement prior to use). In another large trial in cranioplasty patients ($n = 103$), an overall infection rate of 5.8% was achieved.⁴⁴⁶

Norian SRS/CRS

Norian (Synthes, Inc.) is a unique carbonated calcium phosphate that mimics the inorganic phase of bone. Conferring solubility at a low pH, Norian has the theoretical advantage of resorption and replacement by true bone.⁴⁴⁷ This calcium phosphate cement is produced intraoperatively by mixing a base powder (monocalcium sulfate, monohydrate, α -TCP, calcium carbonate) and a solvent containing sodium phosphate at room temperature.⁴⁴⁸ After a 5-minute interval, the material becomes implantable, and continues to cure for approximately 24 hours to become a microporous polycrystalline apatite with a maximum compressive strength of 50 MPa and tensile strength of 2.1 MPa. For comparison, the compressive and tensile properties of cancellous bone are 1.9 and 2.42 MPa, respectively.⁴⁴⁸ The commercial product is available in regular and fast-setting formulations.

FDA-approved since 1998, Norian CRS has now been subject to long-term clinical outcome analysis. Providing the largest series specific to this bone cement in the context of craniofacial surgery, Gilardino and colleagues⁴⁴⁹ report a rather substantial complication rate (26% overall) when using this product, regardless of the type of cranioplasty (onlay, full-thickness inlay). The majority of complications were infectious, attributable to the sheer amount of material used, or its use in a contaminated field. Stratifying according to type of cranioplasty (inlay versus onlay), the authors report the following limitations with Norian: (1) increased trending complication rate when >25 cm² inlay defects are reconstructed with this bone cement; (2) statistically significant increased complication rate when onlay constructs were placed in areas of high bacterial contamination (paranasal sinuses). Such results indicate that this bone cement, not dissimilar to others, is likely not osteoconductive, as supported by several experimental studies.⁴⁵⁰

Osteoactive materials

Osteoactive materials include bioactive glass (NovaBone®, Porex Surgical Inc.) and DBM. Composed of silica dioxide, sodium dioxide, calcium dioxide and phosphate, bioactive glass confers its osteogenic properties when these components are mixed together to form an apatite surface layer. This layer recruits and stimulates osteoprogenitor cells to produce cytokines that have an autocrine and paracrine effect. Osteoblasts proliferate and differentiate on this surface, leading to new bone formation. In turn, the particulate glass is resorbed via osteoclastic activity.

The formulation that comprises DBM is based upon the landmark work of Urist and Strates⁴⁵¹ and Reddi and Huggins.⁴⁵² To date, manufacturers produce this bone substitute with the standard methodology: human cadaver long diaphyses are morselized to 250–600- μ m particle sizes, demineralized in 0.6 N hydrochloric acid, and washed with

deionized water, ethanol, and ethyl ether. In contrast to bioactive glass, DBM contains trace amounts of BMP, which makes this biomaterial both osteoconductive and osteoinductive. At baseline, however, DBM alone is hard to handle, making it difficult to apply clinically. In order to improve handling characteristics, manufacturers have added various types of carriers to the formulation (e.g., glycerol, gelatin, calcium sulfate). Therefore, not all preparations of DBM are the same. To this end, Acarturk and Hollinger⁴⁵³ have performed comparative analysis of all the different DBM products. In an athymic rat critical-sized calvarial defect model, they found that there was indeed a differential bone-regenerative effect among the different formulations. One unifying principle was that those formulations that handled better (DBM + glycerol (Grafton, Osteotech, Inc.), DBM + hyaluronan (DBX, Synthes US)) demonstrated statistically significant higher bone formation than other groups, as assessed by histomorphometry. Overall, however, the bone-regenerative capacity was not as robust as the authors predicted, which could be related to not achieving the threshold quantity of particulate DBM required for complete ossification of the defect. There are numerous formulations of DBM that have been utilized for a variety of applications as reviewed by Gruskin and colleagues.⁴⁵⁴

Prefabricated polymers

Methylmethacrylate

An acrylic-based construct, methylmethacrylate^{455–457} forms when a powdered mixture of methyl methacrylate polymer, methyl methacrylate-styrene copolymer, and benzoyl peroxide monomer is combined. The reaction is caustic, leading to an exothermia that approaches 85°C and pungent fumes that are carcinogenic. In fact, the premixing recommendations of this construct recommend use in an approved fume hood. After mixing for 8–10 minutes, the polymerization process yields a rigid, durable material that can be contoured, is radiolucent, and can be fixed rigidly to the cranioplasty site. Advantages of this material include a relatively low cost, possibility of *in situ* contouring, and lack of biodegradation. A prefabricated, customized, modified version of this material (Hard Tissue Replacement, Biomet Corporation, Jacksonville, FL) is composed of polymethylmethacrylate-polyhydroxyethyl methacrylate and available based on preoperative computed tomography data.⁴⁵⁸ This hard tissue replacement polymer has been utilized in cranial defect reconstruction, chin and malar augmentation, and correction of the temporal “hourglass” deformity.⁴⁵⁹ The major drawback to acrylic-based resins, and in particular methylmethacrylate, is the substantial exothermic reaction involved in curing, which *in situ* can lead to severe thermal tissue injury. The cured, rigid substance has a high bacterial adhesion profile, and thus the high incidence of infected cranioplasties when using this substance.

Medpor

A high-density, porous polyethylene construct (pore size 100–250 μ m), Medpor has gained some popularity in the reconstruction of select sites of the craniofacial skeleton. Current applications include nasal/malar augmentation, orbital floor reconstruction, genioplasty, and cranial augmentation. In this last application, Medpor has been found to augment

successfully resorptive areas of the craniofacial skeleton (e.g., temporal fossa). Due to its porous nature, this implant permits native tissue ingrowth and therefore may provide some resistance to infection. Other advantages include the ability for intraoperative contouring, and customized prefabrication based on three-dimensional volumetric data (DICOM) from computed tomography. Despite these benefits, there are clear disadvantages to this material (risk of infection, exposure, extrusion) that limit its use to well-vascularized recipient sites. As with all alloplastic cranioplasties, an irradiated field bears a relative contraindication from the use of this implant. Recently, Medpor has been successfully used in conjunction with 3D modeling for reconstruction of a suprastructure maxillectomy defect.⁴⁶⁰ Indeed, the use of 3D modeling and virtual surgical planning may improve surgical outcomes and aesthetics when using alloplastic implants for complex craniomaxillofacial defects.

Experimental scaffolds

Appreciation for the role and structure of native ECM as well as pitfalls associated with current techniques for bone regeneration have prompted investigation of experimental scaffolds to augment osseous engineering strategies. Biomimetic scaffolds can be used to improve delivery and containment of progenitor cells and growth factors to the defect. These complex 3D structures serve a role analogous to native ECM.⁴⁶¹ Effective scaffolds are biocompatible, exhibit mechanical properties similar to the surrounding tissue into which they are implanted, and support cellular adhesion and proliferation. Additionally, scaffolds must allow for ingrowth of autologous tissue (i.e., be biodegradable). Many experimental scaffolds have been studied, including polymer-based, CaP-based, and composite-based scaffolds. An in-depth review of significant recent research can be found elsewhere.⁴⁴²



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Repair and grafting of peripheral nerve

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SYNOPSIS

- Primary neurorrhaphy remains the gold standard in nerve repair; all other methods of repair are judged in comparison to primary neurorrhaphy.
- Following any mechanism of repair, nerve regrowth occurs at a maximum of 1 mm/day, making distance from end-target muscle the most important prognosticator for recovery.
- Excessive tension will inhibit nerve regeneration, however a small amount of tension to achieve primary coaptation is acceptable.
- In the event of a nerve gap, several options for repair exist including:
 - Mobilization and primary coaptation
 - Interpositional nerve autografting
 - Interpositional nerve allograft (acellular or fresh cadaveric)
 - Interpositional nerve conduit
 - Distal nerve transfer.
- Prognosis following nerve injury is impacted by several factors:
 - Patient age and comorbidities
 - Location of injury (proximal versus distal peripheral nerve)
 - Mechanism of injury (crush versus avulsion versus transection)
 - Timing of repair
 - Method of repair (tension, alignment, scarring).

Introduction

Nerve injuries present a unique problem in patient management due to the prolonged periods of recovery and the necessity of having viable axons reach the end-motor target prior to irreversible atrophy and fibrosis. These patients suffer significant negative impacts including chronic pain, depression, and considerable effect on daily life.¹ In the setting of prognosis, *time is muscle*, with permanent muscle damage occurring as early as one year after denervation. While primary nerve repair and grafting have not changed significantly in the last several decades, there have been several paradigm shifts as understanding of the internal neural topography has improved

and new techniques and products have become available. The gold standard in nerve repair remains primary neurorrhaphy, however in the situation of a nerve gap, other alternatives are necessary to avoid excessive tension, which causes permanent scarring at the repair site. Autologous nerve grafting has been the procedure of choice for addressing a nerve gap, however donor sites are limited and leave deficits. While nerve autografts are considered the “gold standard” for a nerve gap reconstruction, it should actually be considered a “bronze standard” as results are never normal. Other alternatives include acellular nerve allografts, conduits, and nerve transfers. This chapter reviews the various methods of addressing a nerve injury, with emphasis on surgical decision-making, timing, and prognosis.



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Basic science/disease process

Types of nerve injury

As seen in [Table 19.1](#), nerve injuries can be classified based on their degree of damage and the components of the nerve that have been affected. While this method of classification is useful for prognosis and surgical decision-making, the mechanism of injury also provides a useful method of classification that allows for an algorithmic approach to treatment. Nerve injuries can therefore be classified as either open or closed, and then subdivided by mechanism of injury as penetrating injuries, avulsion or crush injuries, or stretch and avulsion injuries.

Penetrating injuries

Penetrating trauma can be a result of sharp or blunt penetration and will often have concomitant injuries to adjacent structures such as blood vessel, tendon, and muscle. A sharp

Historical perspective

The history of nerve injury

A peripheral nerve can be classified in several ways. Historically, the first classification system by Sir Herbert Seddon (1943) was based on gross and histologic anatomical changes rather than mechanism of injury.² He described three types of nerve injuries:

1. Neurapraxia: involves a local conduction block at a discrete area along the course of a nerve.
2. Axonotmesis: implies direct axonal damage.
3. Neurotmesis: implies transection of the peripheral nerve.

In neurapraxic injuries, Wallerian degeneration does not occur and the prognosis is excellent with anticipated recovery of full strength and function. In both axonotmetic and neurotmetic injuries, Wallerian degeneration occurs distal to the site of injury. Recovery is possible within an axonotmetic injury, but Seddon described a degree of scarring and less complete recovery within this type of nerve injury. In neurotmesis, there will be no recovery. Sunderland expanded upon the earlier Seddon classification and emphasized five degrees of nerve injury.³ Mackinnon later went on to include a sixth degree (see [Table 19.1](#)).^{4,5} Understanding the degree of injury is helpful to predict recovery. It is anticipated that a first-degree neurapraxic injury will make a full and speedy recovery. Second-degree axonotmetic injuries will make a full recovery at the classic rate of 1–1.5 mm/day.⁶ Fourth-degree axonotmetic injuries, also known as a neuroma-in-continuity, and fifth-degree neurotmetic injuries do not recover. Third-degree axonotmetic and sixth-degree (multi-level) injuries recover partially for different reasons. The difficulty with surgical correction of a sixth-degree injury is limiting the repair to

fascicles affected by fourth- and fifth-degree damage, and not damaging adjacent fascicles with potential for spontaneous recovery.

The history of nerve grafts

Current practices that account for the success of nerve grafts include the use of small, thin grafts that are cabled when necessary. Historically, when nerve trunks were used as grafts, poor results ensued.⁷ Small, thin grafts revascularize more easily than larger nerves and this contributes to the success of functional outcomes. The maximum length that may be bridged by a nerve graft is controversial. In general, results fall off and are less predictable at lengths greater than 6 cm. However, 20 cm and longer nerve grafts have been used with varying degrees of success.^{8,9} Taylor and Ham introduced free vascularized nerve grafts in 1976 in order to treat these longer gaps.¹⁰ For smaller defects, a vascularized graft and conventional graft do not appear to differ in clinical outcome, however Doi *et al.* recommend using free vascularized nerve grafts when the gap distance is greater than 6 cm with associated soft-tissue loss over the repaired area.¹¹ Currently, the indication for a free vascularized nerve graft is for reconstruction larger-diameter nerve grafts, such as the ulnar nerve, in brachial plexus avulsion injury.^{11–13}

The history of conduits

Biological conduits, including bone, artery, collagen, vein, muscle, and small-intestine submucosa have been used.^{14–17} Biodegradable synthetic conduits such as polyglycolic acid are currently used, while nondegradable nerve guides made from silicone have fallen out of favor.¹⁸ Their major disadvantage is leaving foreign material that potentially causes a chronic reaction with excessive scarring.

Table 19.1 Classification of nerve injury

Seddon	Sunderland	Injury	Recovery
Neurapraxia	Degree I	Conduction block resolves spontaneously	Fast/excellent
Axonotmesis	Degree II	Axonal rupture without interruption of the basal lamina tubes	Slow/excellent
	Degree III	Rupture of both axons and basal lamina tubes, some scar	Slow/incomplete
	Degree IV	Complete scar block	None
Neurotmesis	Degree V	Complete transection	None
	Degree VI (Mackinnon)	Combination of degree I–IV ± normal fascicles	Mixed

laceration, such as from a knife or a piece of glass, will almost always necessitate exploration if a nerve deficit is present on initial clinical examination. The likelihood that the nerve is partially or completely transected is high. These injuries should be explored within 72 hours if distal stimulation using an intraoperative nerve stimulator is needed. In addition, the further from the time of injury, the more difficult mobilization of the proximal and distal ends to coapt primarily becomes. In the event of a penetrating trauma associated with a vascular injury, immediate exploration is warranted. Unfortunately, in significant proximal injuries necessitating arterial reconstruction with or without underlying fractures, a nerve injury can be overlooked due to the more urgent vascular and orthopedic injuries. In these situations, when a nerve deficit is noticed postoperatively, it is unclear if the nerve injury is from the inciting event, iatrogenic during the repair of the other injuries, or secondary to edema or hematoma. While a computed tomography scan or magnetic resonance imaging may be helpful to evaluate for the latter, internal scarring of the nerve may not always be clearly determined.

Blunt penetrating and blast injuries, such as gunshot wounds or injuries due to an incendiary device, are often managed conservatively similar to closed crush and traction injuries. There is potential for spontaneous recovery. Local tissue edema often causes a neurapraxia, which should resolve within 12 weeks. If recovery is not evident on serial clinical examination and electrodiagnostic studies by four months, the algorithm for a crush injury should be followed (Fig. 19.1).

Crush injuries

Crush injuries are common peripheral nerve injuries to the upper extremity. External crush may be complicated by increased internal pressure from hematomas, fractures, and local tissue edema. When minor, this may cause a temporary neurapraxia, but with greater compression, the likelihood of a permanent injury increases. The most severe consequence of a soft tissue crush injury is the progression to compartment syndrome, which is a surgical emergency. Often an early sign of impending compartment syndrome is a decrease in vibration sensibility.¹⁹

While nerves are fairly resistant to injury given their elasticity, a mixed nerve injury can often occur. A more extensive crush injury can cause local tissue damage that contributes more to the loss of function than the original nerve injury. Muscle tissue is the most susceptible to external forces. Even if the injury is not significant enough to cause a compartment syndrome, the local destruction of muscle may lead to muscle necrosis. Tendon and skin are more resistant and can

withstand higher compressive forces before irreversible damage to the cells results.

The nerve portion of a crush injury is usually treated conservatively. Exploration is warranted if nerve recovery does not follow the anticipated pattern of recovery based on distance from injury to end-target muscle. Along with avulsion injuries, the treatment algorithm for a crush injury involves serial clinical examination and electrodiagnostic studies as dictated by the anticipated recovery (Fig. 19.2).

Stretch and avulsion injuries

When the strain on the nerve exceeds a certain limit, the internal structure of the nerve becomes injured without any appreciable external evidence of injury. Nerves that are stretched to the point of avulsing from their proximal origin suggest a high-velocity, or high-impact, injury that is often associated with limb or life-threatening injuries that take precedence over the repair of the nerve. The nerves tend to be avulsed around areas of tethering, such as bony foramina or the spinal cord. If the proximal nerve can be accessed, grafting of the nerve may be possible. For areas such as the cranial nerves or the spinal roots, where the portion proximal to the avulsion is not accessible, reconstruction is typically done by either nerve or tendon transfers.²⁰ The algorithm for treatment of these injuries involves focusing first on the nerve injury, with repair or reconstruction dictated by degree of injury, followed by procedures to augment recovery such as tendon transfers and joint arthrodesis (see Fig. 19.2).²¹

In situations where no distal nerve is accessible, such as avulsions from the neuromuscular junction, implantation of the proximal nerve directly into the muscle to neurotize the muscle is an alternative. Some studies show as good as MRC 4/5 motor recovery 1–2 years after direct nerve to muscle neurotization, however experimental studies do not support these findings; rather, recovery is much less than a nerve coaptation would produce.^{22,23}

Hints and tips

Sharp penetrating injuries with an acute nerve deficit should be explored early (within 72 hours) if stimulation of the distal end is needed to perform a primary neurorrhaphy. Crush and traction injuries should be treated conservatively with serial examination and electrodiagnostic studies at regular intervals based on expected recovery.

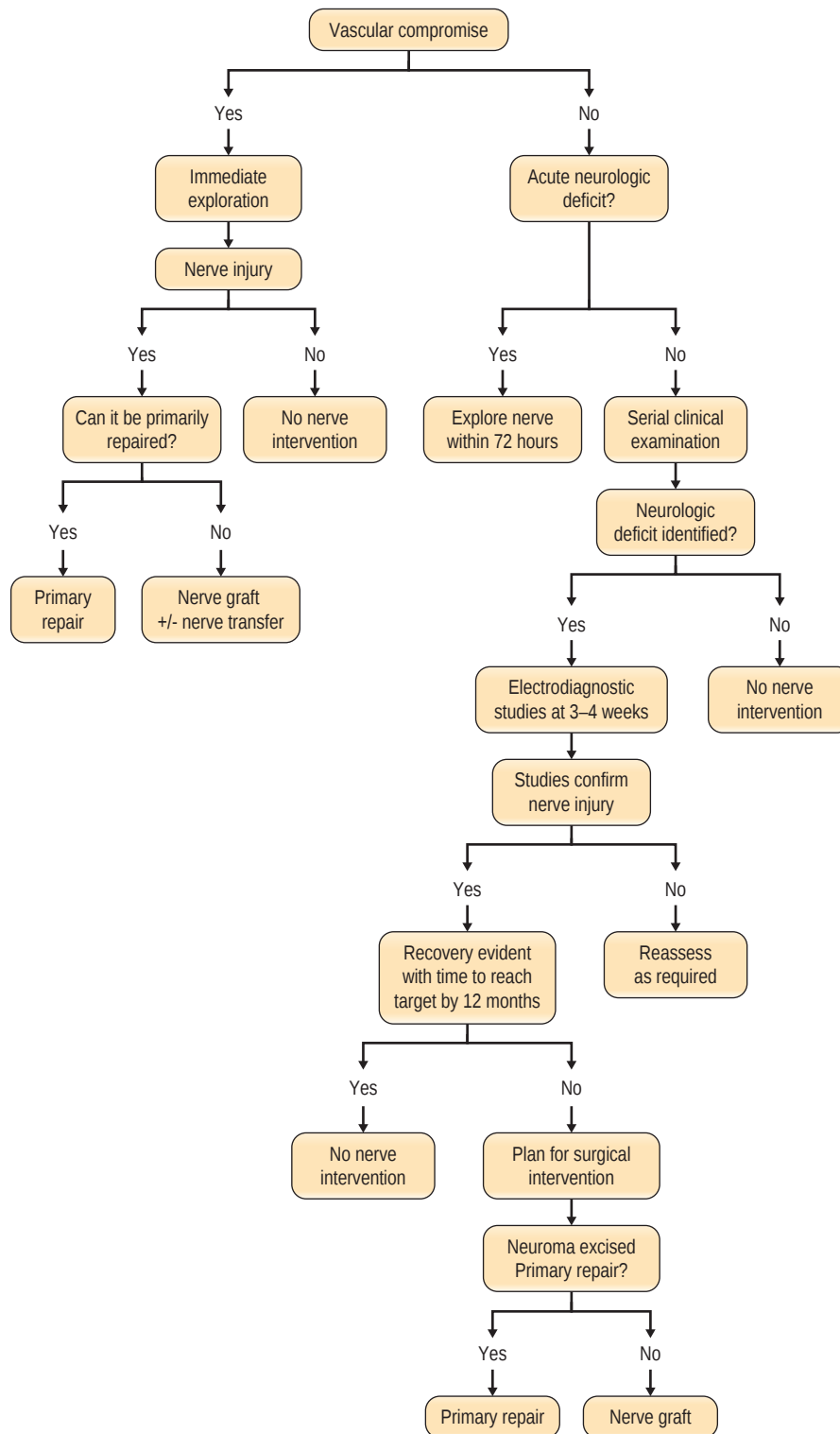


Fig. 19.1 Algorithm for penetrating injury and lacerations.

Diagnosis/patient presentation

A thorough history and physical examination remain the mainstay of diagnosis for a peripheral nerve deficit. A component of experience in recognizing common patterns of nerve injury can facilitate this.

Sensation can be tested using Semmes–Weinstein filaments, two-point static and moving discrimination, or the “ten test”.

The quick and easy “ten test” uses the patient’s own subjective perception to moving light touch to elicit differences in sensation, using the contralateral digit as a reference point.²⁴ This technique is particularly useful in young children, who may have difficulty cooperating with two-point discrimination, or with rapid assessment of a patient being rushed to the operating room for an associated vascular injury.

Motor deficits are recognized by focused examination of all muscle groups in the upper extremity, with patterns

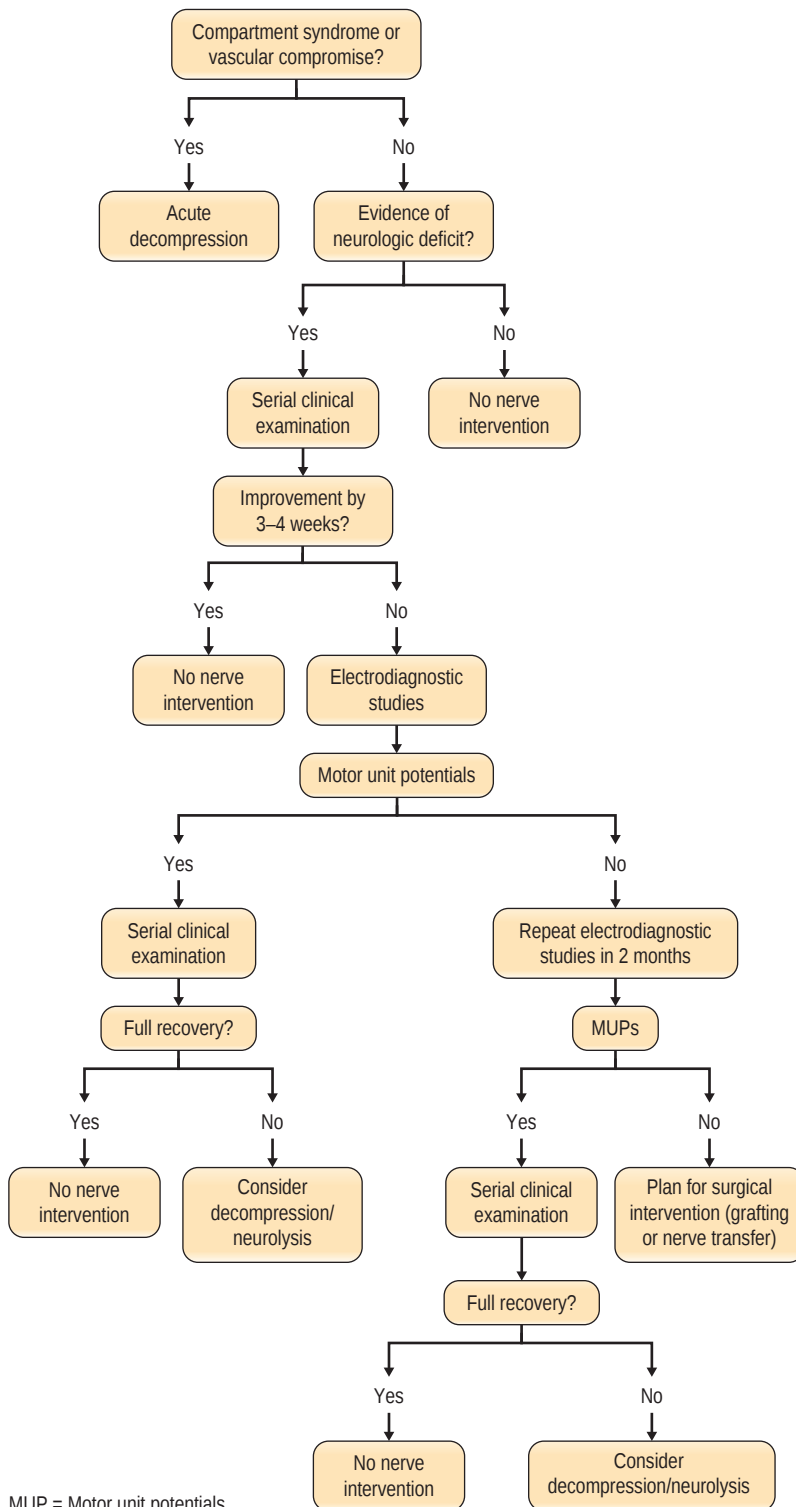


Fig. 19.2 Algorithm for closed traction injury, stretch injury, or avulsion injury.

of weakness or inactivity being used to diagnose the involved peripheral nerve.

In patients with an acute deficit, determination of whether the nerve will recover spontaneously, or whether surgical intervention is required, can often be difficult. The mechanism of injury can assist in preoperative evaluation. Any sharp, penetrating injury should be explored within 72 hours. Similarly, any injury where there is a high index of suspicion for nerve transection should be explored and repaired. The

advantage to early repair, and specifically repair within two weeks, is that the proximal and distal nerve ends have not retracted and primary neurorrhaphy is often possible. Closed traction injuries, partial avulsion injuries, and crush injuries with an associated nerve palsy are more difficult to evaluate. Waiting 3 to 4 months with serial clinical and electrodiagnostic examination is advocated.

The electrodiagnostic signs of an axonotmetic injury, particularly fibrillations and positive sharp waves, may not

be present for at least three weeks from the time of injury, once Wallerian degeneration has occurred. For this reason, electrodiagnostic studies at the time of injury are not recommended except to document any pre-injury pathology. Regular electrodiagnostic testing, and specifically electromyography, is advocated due to the fact that EMG changes precede clinical recovery by months. In closed injuries, if there is no evidence of recovery in the form of motor unit potentials (MUPs) by 3 to 4 months, surgical exploration and reconstruction are warranted. The presence of MUPs by three months suggests at worst a third-grade injury, which should recover spontaneously at the rate of 1 mm/day.

The role of imaging in the clinical investigation of nerve injuries is more controversial. New ultrasound machines have the resolution to detect digital nerve neuromas, however these studies are still largely investigational and are highly operator-dependent. There is some early evidence that ultrasound is more sensitive (93%) than MRI (67%) with similar specificity (86%), however this is more typically in the setting of nerve pathology.²⁵

Hints and tips

Clinical evaluation at the earliest opportunity, followed by serial clinical examination and electrodiagnostic studies, are critical in the diagnosis and assessment of a nerve deficit. Recognizing patterns of recovery or the lack thereof can facilitate decision-making regarding timing an operative intervention.

Patient selection

Nerve injuries often occur in the setting of concomitant injuries and sometimes multi-organ system trauma. Unlike in the elective surgical patient, there is little ability to select an ideal patient.

The importance of recognizing the impact of concomitant injuries cannot be overstated. Patients should be stabilized, with repair of life-threatening injuries (such as vascular laceration) taking priority. Bony fixation and fracture immobilization generally precede nerve repair, as the possibility of iatrogenic injury to the microscopic nerve repair is high.

Wherever possible, nerve repair should be performed during daytime hours, with proper operating equipment and well-versed operating staff. An operating microscope and loupe magnification should be used to explore and identify cut nerve ends. Experienced surgeons will facilitate surgical decision-making based on method and level of injury.

Treatment/surgical repair

Prompt, tension-free, primary neurorrhaphy is universally held as the ideal repair, and multiple animal studies support the idea that single nerve repair results in a better outcome over a nerve graft.²⁶ With each repair site, a percentage of fibers are lost, therefore fewer neurorrhaphies ensures a greater percentage of proximal nerve axons reaching the target endplates. Some investigators believe that as many as 50% of regenerating sensory or motor axons may never reach

the correct end-target.²⁷ Recent studies also show that Schwann cell senescence occurs as graft length increases.

In the event that a primary repair is not possible, mobilization of the proximal and/or distal nerve ends may overcome a small, less than 5 mm, gap because of the elastic property of the nerve.²⁸ If, however, a repair is performed in the face of tension and contamination, unfavorable scarring will occur. In this situation, two neurorrhaphy sites are preferable to a single neurorrhaphy under unfavorable conditions.^{29,30} If primary repair by mobilization cannot be achieved, there are several techniques to address the resultant nerve gap (Table 19.2).^{31,32}

Conduits

The use of conduits to bridge major nerve gaps has been described, but has largely fallen out of favor. For non-critical, small diameter, sensory deficits less than 3 cm, conduits may serve as a potential option. Biological and synthetic conduits are available. Using this method, protective sensation, and in some cases good sensation, have been restored.³³ When using a conduit, placing a small portion of the proximal nerve into the conduit to serve as a source of Schwann cells is recommended.³⁴ More often, the conduits are now used as nerve wraps for protection of a primary neurorrhaphy, however this can be cost prohibitive. Seprafilm[®] adhesion barrier (Genzyme, Cambridge, MA) has been used by the authors placing a small piece above and/or below the repair.

Nerve grafting

Autologous nerve grafting

The most common technique for addressing a nerve graft is interpositional nerve grafting. Autologous nerve grafts are the gold standard or better termed bronze standard. The nerve graft serves as a guide for the axon as it regrows towards the distal stump (Fig. 19.3). Although the sural nerve is most commonly used as a donor nerve, our algorithm for selecting autograft donors has evolved away from this donor (Table 19.3).^{32,35–37} Wherever possible, donor nerves within the affected extremity and available through the same surgical incision are selected.³⁸ Experimental studies comparing motor, mixed, and sensory grafts support the idea that motor and mixed nerve grafts achieve better regeneration across the repair.^{39,40} Donor motor nerve grafts, however, are in more limited supply, and in clinical practice, the branch from the obturator to the gracilis and the distal anterior interosseous nerve are the two motor grafts that cause the least morbidity. The obvious downsides of autologous grafting are the limited number of donor nerves available and the resulting donor site morbidity.

Acellular nerve graft

Acellular human processed nerve allografts (ANA) have been introduced as a method for spanning the nerve gap. Initial clinical trials show that recovery for small sensory gaps is better than that for conduits and more comparable to autografts.⁴¹ This human tissue retains its three-dimensional structure, including epineurium, fascicles, endoneurial tubes and laminin, and it is believed that the scaffold allows for repopulation of the host cells, similar to autologous tissue (Fig. 19.4).

Table 19.2 Options for management of the nerve gap

	Advantages	Disadvantages
Nerve autograft	Gold standard for reconstruction Schwann cells in extracellular matrix	Second operative site Results in donor sensory loss Potential for neuroma formation/pain Sensory nerve autografts do not support motor regeneration as well as motor or mixed sensorimotor nerves Limited available length
Allograft	Can potentially allow functional recovery equivalent to autograft No donor site morbidity	Requires patient systemic immunosuppression (~18 months) Patients vulnerable to opportunistic infections
Conduits	Circumvents adverse effects of autografts and allografts Guides regenerating nerve to intended target	Length limitation (<3 cm) Only for small-diameter sensory nerves No Schwann cells No matrix Expensive
Acellularized graft	Retains scaffolding matrix of nerve tissue Nonimmunogenic and inert Biological substrate for nerve regeneration without need for immunosuppression	Length limitation (<5 cm) No Schwann cells Only for small-diameter nerves Very expensive
End-to-side	No length limitation	Poor sensory results Motor requires donor neurectomy
Reverse end-to-side	Augment partial motor/sensory nerve injury	Requires knowledge of topography Requires knowledge of expendable donors May need nerve autograft or acellular graft
Nerve transfer	Earlier motor/sensory target recovery	Requires expendable donor Requires motor (sensory) re-education Requires knowledge of nerve topography

These grafts shorten operative time and eliminate donor deficit, however they are expensive. The ANA handles similarly to an autologous graft, and may be secured via suture or sealant. ANAs have been shown to be superior to an empty conduit, however they are inferior to autograft.⁴²

In the authors' practices, ANAs have largely replaced the use of conduits, and are appropriate for small-diameter, noncritical short (less than or equal to 3 cm) nerve gaps. These grafts are never used for large-diameter gaps, motor defects, or used to bridge a long gap. ANAs are dependent on proliferating Schwann cells from the host tissue. Axonal regeneration and functional recovery have been demonstrated to decrease with graft length and are inferior to autograft at all lengths.⁴³ The mechanism appears to be in part Schwann cell senescence induced by ischemia and cellular proliferation. Transplanting Schwann cells into ANA has been shown to improve functional regeneration closer to isograft levels in a laboratory setting.⁴⁴

ANAs undergo differing processing methods and there is some evidence that this may impact functional outcome. Three models of acellular nerve allografts were examined in a rat model, and the differential processing for removal of cellular constituents in preparing the ANAs were found to affect recovery *in vivo*.⁴⁵

Nerve transfers

Over the past decade, there has been a paradigm shift towards the use of nerve transfers in the restoration of function

following nerve injury. In 2011, Garg *et al.* performed a systematic analysis that demonstrated that when international data were pooled, nerve transfers were strongly superior to nerve grafting in upper brachial plexus injuries.⁴⁶

The principles of nerve transfer are to use expendable, pure donor fascicles. Nerves with redundant fascicles or branches make excellent donor nerves. Because the nerve transfer does not rely on the amplitude and excursion of the tendon muscle unit, unlike tendon transfers, and is not limited to one function, nor a straight line of pull, the muscle-tendon balance can be maintained. The major advantages of a nerve transfer over that of a tendon transfer are that: (1) nerve transfers can restore sensibility in addition to motor function; (2) a nerve that innervates multiple muscle groups can be restored with a single nerve transfer; and (3) the insertion and attachments of the muscle are not disrupted, thus the original muscle function and tension are maintained. Synergistic nerve transfers are preferred because of the ease of rehabilitation.

Nerve transfers are advantageous compared to long nerve grafts because they have the ability to convert a proximal, high-level nerve injury into a low-level nerve. This is particularly important in high median and ulnar nerve injuries to achieve restoration of hand function. Nerve transfers facilitate operating outside the zone of injury and have the advantage of a single neurorrhaphy.

Nerve transfers are possible because of the redundancy existing in proximal, mixed nerve fibers. Knowledge of the internal topography facilitates the separation of fascicular groups even in the proximal extremity; fascicular groups run

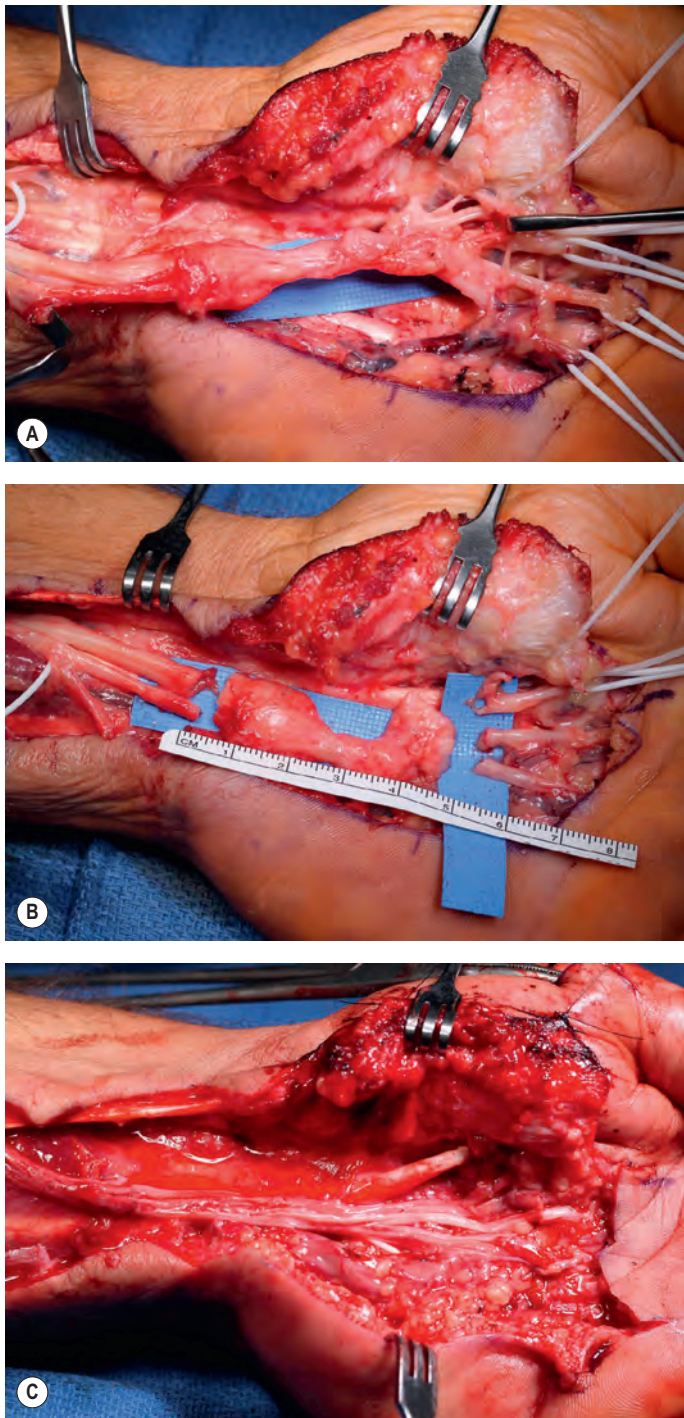


Fig. 19.3 Nerve autograft. A patient presenting with (A) a neuroma-in-continuity of the median nerve at the level of the carpal tunnel. The neuroma (B) was resected and treated with (C) cable grafting using medial antebrachial cutaneous nerve (MABC) as a donor.

adjacent to each other in a consistent pattern within the larger nerve itself.⁴⁷ Intraoperative electrical stimulation with a hand-held device (Vari-Stim®, Bio-Medicine) can be used to identify and confirm specific function.

Bioengineering

The need for a bridge or scaffold that successfully allows regenerating axons to reach the end-target muscle in the

setting of a nerve gap has been long recognized. While multiple bioengineering projects have started investigating a solution to this challenge, none so far has succeeded.^{48–51}

Johnson *et al.* have recently described the characteristics of an ideal tissue-engineered construct, including the goals of creation.⁵²

Method of repair

Timing of repair

Patients with an index of suspicion for potential nerve transection are taken to the operating room within 72 hours for exploration and primary repair. Nerves repaired within 48 hours are considered repaired primarily. Delayed repair occurs between 2 and 7 days, and requires freshening of the distal and proximal ends prior to coaptation. Nerves repaired after the first week are considered to be secondarily repaired. While these times are arbitrary, it is clear that the longer the

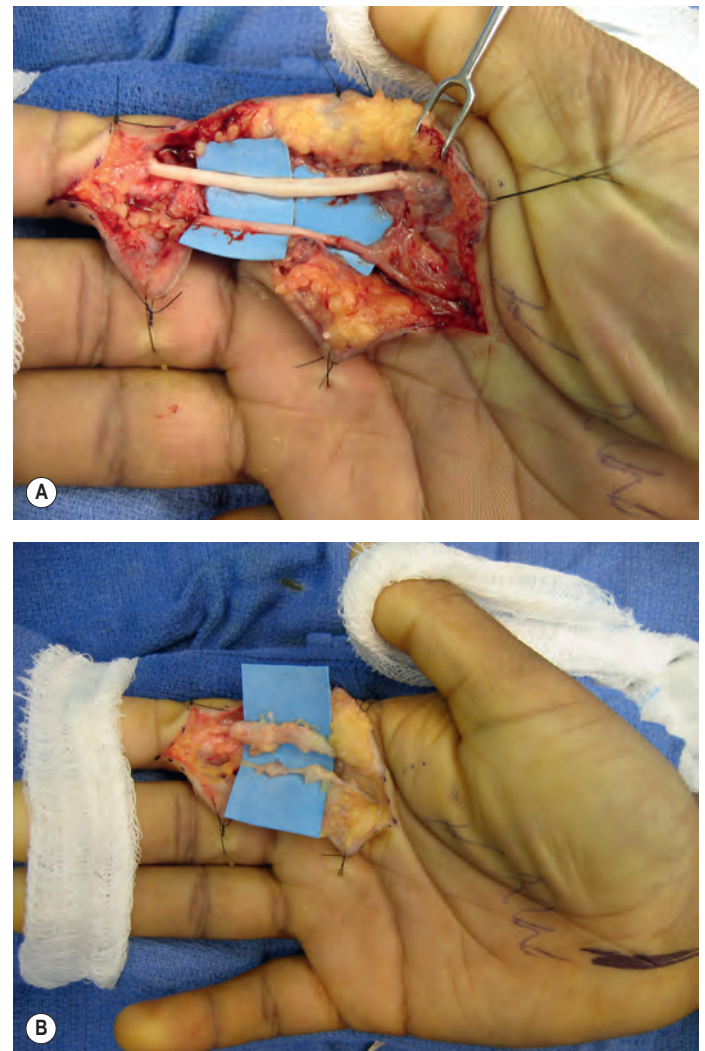


Fig. 19.4 The nerve allograft (A) can be chosen to match the width of the injured nerve. Here are two different size grafts that were sutured in place with 9-0 nylon sutures after resection of two digital neuromas (B).

Table 19.3 Characteristics of nerve autograft donors based on published literature

Donor nerve	Harvestable length	Fascicle count	Cross-sectional area	Disadvantage	Advantage
MABC	Up to 28 cm	7–10	2–3.15 mm ²	• Medial arm scar	• Long length and larger caliber nerve suitable for larger nerve gaps and/or multiple cables required • Can minimize donor morbidity with end-to-side repair of distal end MABC to median nerve
LABC	5–8 cm	4–9 5–18 6–15 5–7	1.3–1.8 mm ²	• Visible forearm scar	• Good for short gaps • Good size match with digital nerve • Usually injured with SBR and therefore good nerve graft for SBR injuries • Dermatome overlap with SBR reduces donor morbidity
TWM ^a	24.5 cm	2–13	4.43 mm ²	• Sensory loss in hand (non-critical)	• Easy access through volar distal forearm incisions
PCM ^a	Mean length 5.24 cm			• Sensory loss in palm	• Easy access through volar forearm incisions
DCU ^a	Up to 26 cm • Dorsal-ulnar hand divisions, 5–6 cm		2.4 mm ² at origin	• Sensory loss to dorsal-ulnar hand and digits	• Useful if ulnar nerve already injured and working in same operative site
AIN ^a		3–5	0.6–0.7 mm ²	• Deep dissection into pronator quadratus • Short segment available	• No sensory loss • Good size match with digital nerves
PIN ^b	2.5 cm	2	0.5–0.8 mm ²	• Visible dorsal incision • Small diameter graft	• No cutaneous sensory loss
SBR ^a				• Potential for hypersensitivity in donor territory	• Consider if radial nerve already injured
Sural	30–50 cm	9–14 MSC 1–3 LSC 5–7	2.5–4 mm MSC 1.5 LSC 1.5	• Positioning difficult • Requires second extremity	• Long length
Obturator	9.9–13.6 cm 11.5 cm average	2–4		• Loss of gracilis as possible future free functional flap	• No sensory loss • Expendable motor nerve graft

AIN, anterior interosseous nerve; DCU, dorsal cutaneous branch of ulnar nerve; LABC, lateral antebrachial cutaneous nerve; LSC, lateral sural cutaneous; MABC, medial antebrachial cutaneous nerve; MSC, medial sural cutaneous; PCM, palmar cutaneous branch of median nerve; PIN, posterior interosseous nerve; SBR, radial sensory nerve; TWM, third webspace branch of median nerve

^aUsed as non-critical portion of injured nerve

^bTerminal branch

(From Poppler LH, Davidge K, Lu JC, et al. Alternatives to sural nerve grafts in the upper extremity. *Hand (N Y)*. 2015;10:68–75.)

time from injury, the less likely that a primary neurorrhaphy can be achieved, even with significant mobilization of the proximal and distal nerve ends.

Tension

Excessive tension across a nerve repair is known to increase the scarring at the coaptation site, thereby impairing axonal regeneration. In an uninjured nerve, a 15% strain of the nerve causes a reduction in microvascular flow and a delay of peak velocity.⁵³ Clinically, the tension across a repair is never measured, however inseting with any tension is

meticulously avoided. The authors also denounce postural manipulation of the extremity to facilitate tension-free repair, as this increases the likelihood of dehiscence and stiffness due to immobilization.²⁹

Type of repair

The suture diameter is clinically selected based on the size of the nerve. Giddins *et al.* demonstrated in a cadaveric study that 9-0 nylon was the optimal suture to acutely repair the median nerve.⁵⁴ At a lower tension, 10-0 nylon sutures snapped and 8-0 nylon sutures pulled out of the nerve tissue.

Several surgeons advocate for the use of fibrin glue, in place of sutures, especially when there is no tension. Laser energy for epineurial coaptation has been investigated, but causes heat damage and decreased tensile strength. The gold standard remains microsuture under the operating microscope. The authors routinely use a combination of suture and fibrin glue.

Epineurial repair is the preferred method of coaptation once the severed ends are surgically freshened. External markers such as a vessel on the surface and matching the fascicular patterns are used to align the fascicles without overlapping (Fig. 19.5). For major peripheral nerves, an argument for perineurial repair can be made to improve alignment of the larger fascicular groups individually, however clinical studies support both techniques as equally effective as long as the fascicles were not overlapped (Fig. 19.6).⁵⁵ The disadvantage of perineurial repair is that the extensive dissection and the permanent intraneural stitches can lead to increased fibrosis.⁵⁶ In practice, it is often difficult to align the fascicles accurately, as trauma, edema, and scarring can distort the normal topography.

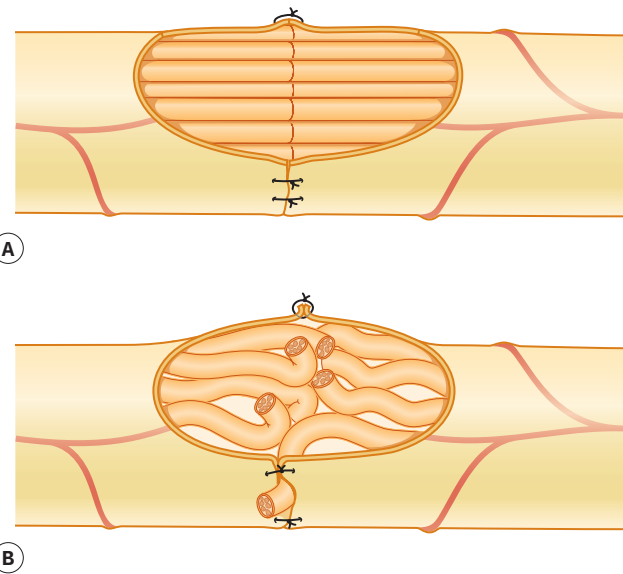
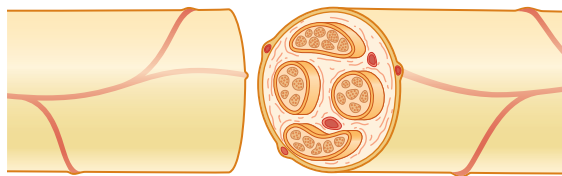
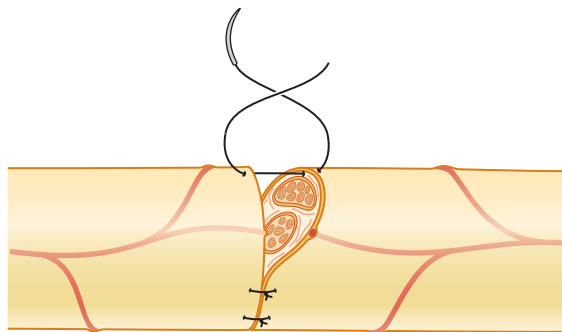


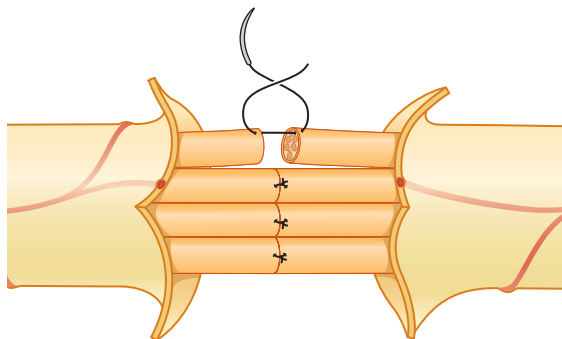
Fig. 19.6 Good alignment of the fascicles (A) is crucial to optimal outcome, whereas bunching and overlap (B) produces an inferior result.



(A)



(B)



(C)

Fig. 19.5 Schematic depicting an epineurial (B) versus perineurial (C) repair after transection of the nerve (A). The native artery and the fascicular pattern are used to align the neurorrhaphy properly. The least number of epineurial sutures using 9-0 nylon is used.

Hints and tips

Using topical landmarks such as longitudinal vessels or fascicular groups for orientation, and the least number of sutures possible to achieve tension-free epineurial repair through gentle, full range of motion, is the optimum method of neurorrhaphy.

Orientation of repair

The majority of nerve repairs are performed in the classic end-to-end fashion. This is irrespective of primary neurorrhaphy or nerve grafting. The role of end-to-side repair continues to be debated. Certainly, end-to-end repair continues to be recommended for all motor, mixed nerves, and sensory nerves in critical distributions. End-to-side repairs for noncritical sensory deficits are acceptable given spontaneous sprouting of sensory nerves. Motor nerves, however, do not spontaneously collaterally sprout; instead, regenerative sprouting occurs following axonal injury proximal to the repair.⁵⁷

The supercharge end-to-side (SETS) technique is used to facilitate early motor axons reaching the target endplates while awaiting proximal regrowth from a high-level injury. This is particularly useful in proximal Sunderland second-degree and third-degree injuries, where long regeneration distance yields prolonged time to muscle reinnervation and suboptimal functional recovery.⁵⁸ The validity of this method of transfer has been confirmed in an animal model.⁵⁹ The classic example would be to perform an anterior interosseous SETS procedure to the ulnar motor branch in the setting of a high ulnar nerve injury, where some recovery is anticipated.

Intraoperative nerve stimulation

A hand-held disposable nerve stimulator may be used to facilitate intraoperative decision-making. While uncomplicated,

clean transections may be equally able to be aligned using topical surface landmarks, in closed traction injuries, especially of the brachial plexus or injuries to larger mixed peripheral nerves, formal intraoperative stimulation may help to identify distal segments. This is also useful if the nerve is injured at several segments along its length, or in the case of partial brachial plexus injury.

When preoperative electrodiagnostic studies have been equivocal, or to ensure that additional recovery has not occurred between testing and surgical repair, the results of intraoperative stimulation may affect the surgical plan.

The hand-held nerve stimulator will provide information about distal motor fascicles, but will not be useful for sensory deficits. The stimulator can also be useful to confirm the identity of redundant nerve fascicles for potential nerve transfer.

Postoperative care

After tension-free primary neurorrhaphy or grafting, no immobilization is theoretically required because the extremity has been taken through full range in the operating room prior to closure. Immobilization for up to 7 days protects the coaptation as the proximal axons grow across the repair site, and the authors use this strategy. Early, protected range of motion, however, is critical for neural gliding and decreased scarring.⁶⁰ Protected range of motion is started within 72 hours for most patients.

In patients with concomitant injuries, the postoperative protocol is guided by the injury and is often difficult to rehabilitate. For example, in a zone 2 volar finger injury where both nerves and tendons are transected, the flexor tendon rehabilitation protocol takes precedence over the nerve rehabilitation, as the nerves can be readdressed at a later time if necessary. In the case of fractures in addition to nerve or soft-tissue injury, the bony fixation takes precedence.

Postoperative pain management is a critical part of the broader treatment of a patient with a nerve injury, and can dramatically affect outcome. Many patients complain in the postoperative period of paresthesia, burning, or electrical shocks. These symptoms can extend beyond the zone of injury. Most of these symptoms can be controlled with neurotropic medications such as nortriptyline, or pregabalin. In some patients, the recovering nerve pain is so severe that they require significant narcotic and neuroleptic medications and the involvement of a pain specialist becomes paramount to managing the associated chronic pain these patients experience. Anxiety and depression should also be addressed and treated.

Physical therapy and occupational therapy continue for an extended rehabilitation period to prevent joint contracture, to provide sensory and motor re-education, to fabricate and adjust splints, and to monitor progress.

Prognosis and outcomes

Prognosis

Several factors will affect the success of a nerve repair. These factors can be further subdivided into patient-related factors, injury-related factors, and repair-related factors.

Patient-related factors

The age of the patient seems to be the most predominant patient-related factor. We know from historical data that nerve repairs in children and young adults, both sensory and motor, yield better results than in adults. In part, this is due to the fact that children are smaller, and thus the nerve regeneration rate of 1 mm/day allows axons to hit the motor endplates in a shorter period of time. Children also demonstrated faster and more adaptable brain plasticity, making recovery from injury significantly faster.

Injury-related factors

The degree and type of injury affect prognosis and outcome. Proximal injuries, which often involve mixed nerves containing both motor and sensory, are more difficult to reconstruct and are located further away from target endplates. Crush and avulsion injuries are more likely to have associated soft-tissue injuries and thus tend to be worse than sharp injuries occurring at the same level. The internal damage of a nerve is often underestimated acutely and poor recovery is usually a result of repair within the zone of injury when re-explored.

Repair-related factors

The timing of repair historically revealed that earlier repair led to better prognosis, most likely because a primary neurorrhaphy was possible. Good prognosis is expected if the repair occurs within six months and the best results occur if the repair is performed within three weeks. In general, functional recovery (FR) is inversely proportional to the time of denervation and directly proportional to the number of motor axons reaching the target endplate. "Time is muscle."

$$\text{FR} \propto \frac{\text{Number of motor axons reaching target endplate}}{\text{Time of Denervation}}$$

Hints and tips

There are a number of factors affecting prognosis following nerve injury. In general, the most important factor is getting as many motor axons to the target endplate in the shortest period of time as possible.

Outcomes

The outcomes achieved with peripheral nerve repair are largely related to the prognostic factors discussed above. Sharply transected isolated distal injuries to isolated motor or sensory nerves do significantly better than more complicated injuries.

Several methods to potentially improve outcomes have been investigated. Recent interest in pharmacological therapies to augment axonal regeneration and overcome inhibitory signals has led to basic science investigation in this area.⁶¹ The role of senescent Schwann cells is another potential area to target.⁶¹

Secondary procedures

Nerve repair, either primarily or with nerve grafting or transfer, often obtains good surgical outcomes when the damage is isolated to the nerve and the injury is a clean transection. In other settings, however, a wide zone of injury or concomitant injuries make outcomes less satisfactory.

There are a number of potential secondary procedures that may improve function and can be performed at a later date. Decompression at known tight spots along the length of a recovering nerve can improve axonal regeneration, especially if re-growth has stalled. Distal nerve transfers can be performed simultaneously to supercharge or “babysit” the recovering muscles, or can be performed at a later date if grafting has failed, assuming that the nerve will reach end-target origin by approximately 12 months (Fig. 19.7).

Tendon transfers are an extremely useful adjunct to the management of significant nerve injuries, and their importance should not be overlooked. In patients who are not good candidates for lengthy nerve grafting procedures or who will not be compliant with, nor able to cooperate with, post-nerve-transfer rehabilitation, tendon transfers remain the standard of care. Certain tendon transfers, such as radial nerve transfers, are typically more successful than nerve transfers and return to activity is much faster following a period of immobilization for tendon healing.

Summary

Primary neurorrhaphy remains the gold standard for all nerve repair techniques, with autologous nerve grafting being the gold standard for bridging a nerve gap. Since the implementation of a nerve allograft in 1870 by Philipeaux and Vulpian, significant contributions regarding suturing technique, neural topography, and the biology of nerve reconstruction have transformed the way we approach nerve reconstruction. While primary neurorrhaphy and autografts are the most common methods for repair, several newer options are at our disposal. Nerve transfers have revolutionized our approach

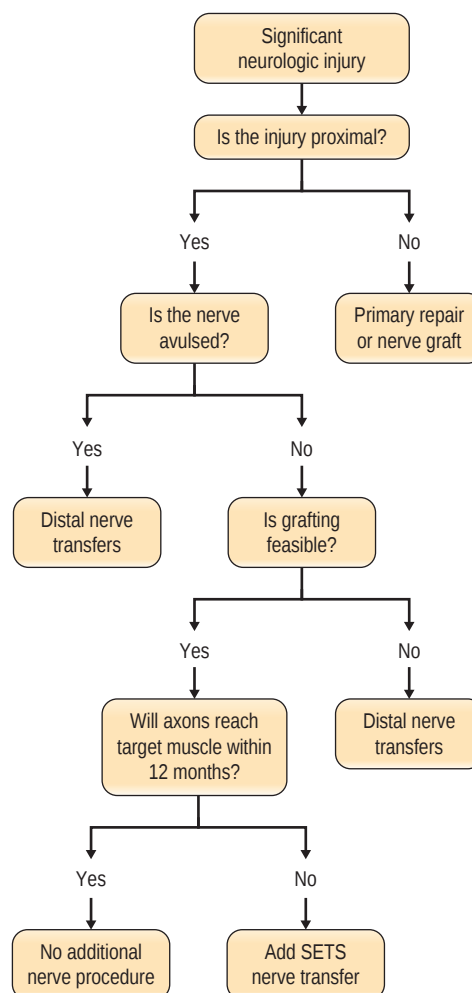


Fig. 19.7 Algorithm for incorporating nerve transfers into the management of a nerve injury. SETS, supercharge end-to-side.

for treating devastating brachial plexus and high-level peripheral nerve injuries, converting them to lower-level injuries and allowing us to operate outside the zone of trauma. Bioengineering continues to be a long-term goal, however this is not currently an option.

Access the complete reference list online at <http://www.expertconsult.com>

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Reconstructive fat grafting

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SYNOPSIS

- Fat grafting is an important technique for tissue repair and/or augmentation in both reconstructive and aesthetic plastic surgery.
- Fat grafting can be used as a minimally invasive adjunct to restore volume and rejuvenate tissues lost secondary to aging, trauma, or disease.
- The biology and principal components of adipose tissue are reviewed with specific focus on adipose-derived stem cells.
- The safety of fat grafting – with specific focus on oncologic implications – is reviewed from both a basic science and clinical standpoint.
- Numerous aesthetic and reconstructive problems can be addressed with fat grafting, and patient selection remains vitally important.

Introduction

Autologous fat grafting has become a common technique for addressing volume and contour abnormalities in plastic surgery, demonstrating efficacy in both aesthetic and reconstructive procedures. Although early use of fat grafting was largely an aesthetic adjunct, recent advancements have made fat grafting an attractive alternative for many reconstructive challenges. A survey conducted in 2013 showed that approximately 70% of plastic surgeons have incorporated fat grafting into their clinical breast practice.¹ Fat grafting has been used successfully for facial rejuvenation, breast augmentation, mitigating radiation damage, breast capsular contracture, post-traumatic deformities, congenital anomalies, and burn injuries;^{2–8} the techniques continually evolve and novel applications rapidly emerge. Autologous fat grafts have numerous beneficial characteristics for reconstruction including: low donor site morbidity, simplicity of procedure, low cost, and resultant living autologous tissue at the site of treatment. Additionally, grafted fat has appealing bioactive factors. Cannula adipose tissue particles include adipose stem cells (ASCs) or preadipocytes, fibroblasts, vascular endothelial

cells, and a variety of immune cells.⁹ It has become apparent through extensive research in the past decade that stromal vascular fraction cells and the adipose stem cells within can improve fat graft survival, largely through their angiogenic properties.^{10,11} Applications for cell isolates from adipose tissue are also finding applications in the fields of tissue engineering and regenerative medicine. Basic science research continues to uncover cellular elements critical for inclusion in fat grafts, which will ultimately lead to modifications and enhancement of existing techniques for improved long-term outcomes.



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Basic science

Adipose tissue: structure and physiology

Adipose tissue is primarily comprised of large lipid-laden adipocytes, which are surrounded by various stromal vascular cells, each with a unique role. Stromal vascular cells include fibroblasts, immune cells, pericytes, and endothelial cells. The extracellular matrix that interconnects adipocytes and forms the fat lobules within adipose tissue provides the structural framework of adipose tissue. There are two general types of adipose tissue: brown fat and white fat. In humans, brown adipose tissue is predominantly found during the neonatal period and is responsible for generating thermogenesis from triglycerides. Brown fat deposits do not appear to play a significant role in human adult metabolism, although recent research has begun to emerge on the importance of brown fat.^{30,31} The discussion here will be limited to the role of white fat, as it is used exclusively for fat grafting procedures.

White fat is involved in a variety of physiologic roles including the storage of energy-rich triglycerides,

Historical perspective

The first clinical report of fat grafting was in 1893 by German surgeon Gustav Neuber when he harvested adipose tissue from the arm and corrected a depressed facial scar resulting from osteomyelitis.¹² This was quickly followed by a report 2 years later by Vincenz Czerny, who transferred a lipoma from the buttock to correct a post-surgical breast deformity.¹³ Though state of the art for that time, fat grafting was ultimately considered difficult and too time consuming with unpredictable results.

Looking for a solution to these problems, Eugene Holländer first injected fat through a small diameter cannula.^{14,15} However, considerable reabsorption of the fat resulted. Later, in 1919, Erich Lexer published a two-volume book dedicated to the technique of fat grafting.¹⁶ In this book, he presented a wide variety of conditions such as depressed scars, breast asymmetry, knee ankylosis, tendon adhesions, and micrognathia that he successfully treated with fat grafting. Charles Miller in 1926 described the injection of autologous fat for the correction of facial folds and wrinkles.¹⁷ Despite some early favorable results, fat grafting on the whole remained unpredictable and again fell out of favor.

It was not until the 1950s, when Lyndon Peer systematically studied the gross and histologic appearance of transplanted fat, that an understanding and improved predictability of fat grafting began to emerge.¹⁸ He demonstrated adipose grafts lose about 45% of their weight and volume at one year. Fat cells that survive transfer appeared to maintain their native volume. Improper handling of the fat prior to and during transplantation decreased survival of the graft. He also demonstrated that graft size plays a role in overall survival. A graft the size of a walnut was found to lose volume more rapidly than multiple smaller grafts of similar weight, due to increased surface area of the smaller grafts. Revascularization,

seen microscopically, was noted by Peer to be essential for fat achieving graft survival.

With the advent of liposuction in the 1980s by Fournier and Illouz, there was a renewed interest in fat grafting.^{19,20} Fat was now a byproduct of a popular procedure and stood in the ready, just waiting for clinical application. Early results of grafting lipoaspirate were only partially successful; the thought at the time was that still better preparation of the fat was needed for survival. Chajchir and Benzaquen made some initial recommendations based on their own favorable results.²¹ There was still great confusion as to what really worked until the 1990s, when Coleman perfected his standard technique. This technique, called structural fat grafting, emphasizes gentle extraction of fat, centrifugation, and serial small volume injections in multiple tissue planes. Coleman has used this technique for almost 30 years and has repeatedly documented durability of fat grafting performed with his method.^{22–25} Numerous researchers have since built upon the work of Coleman and begun to lay the scientific foundation for emerging adipose technologies in the fields of tissue engineering and regenerative medicine.

Although, early reports of fat grafting by Neuber, Czerny, and Holländer as far back as the 19th century demonstrated the potential results achievable with fat grafting for facial and breast reconstruction,^{12–14} fat grafting was not widely accepted until the 1990s. Despite early successes, subsequent reports were met with varying levels of failure, often associated with unpredictable fat resorption.^{26,27} Beginning in the early 1980s, several successful reports of fat grafting were published, and fat grafting increased in popularity once again.^{20,28,29} Plastic surgeons began to recognize the importance of the technical aspects used in harvesting, processing, and injecting fat in order to achieve successful outcomes. Coleman substantiated these claims with his introduction of structural fat grafting in the 1990s, and others have since begun to lay the scientific framework and principles underlying successful fat grafting.

cushioning of vital structures and organs, maintenance of metabolic homeostasis, immune regulation, reproduction, and angiogenesis.^{32–35} The imbalance of adipose tissue resulting in either too much fat, such as in generalized obesity, or too little fat, such as in genetic or acquired lipodystrophies and aging, is an increasingly prevalent problem worldwide. Associated disorders are generally linked with physiologic derangements in insulin metabolism, triglyceride and cholesterol stores, as well as generalized insults to end organs involved in these pathways. The increased recognition of these problems has highlighted the need for a more complete understanding of adipose biology.

Adipose tissue influences metabolic homeostasis through production of assorted hormones, cytokines, growth factors, and other peptides. Factors secreted by adipose tissue are involved in a broad spectrum of physiological processes and molecular pathways including: lipid and steroid metabolism, growth factor signaling, protein binding, cytokine signal transduction, vasoactivity, eicosanoid activity, alternative complement system activation, and extracellular matrix deposition. These effector molecules, termed adipokines, exert their influences in endocrine, paracrine, and autocrine manners. Major adipokines leptin and adiponectin are implicated in obesity and function by regulating appetite and energy expenditure.^{32–35} Tumor necrosis factor- α (TNF- α), interleukin-8 (IL-8), and interleukin-6 (IL-6) are all increased in obesity; they function as proinflammatory cytokines promoting increased insulin resistance. In addition, type 1 plasminogen activator inhibitor (PAI-1) is also increased in obesity and functions to promote thrombosis by inhibiting fibrinolysis, acting as a main endogenous regulator of the coagulation system.³⁶

Adipocyte differentiation begins with the transformation of mesenchymal stem cells into adipoblasts, preadipocytes and, finally, mature lipid-synthesizing, lipid-storing adipocytes. Preadipocytes bear striking resemblance to early fibroblasts in terms of their cellular architecture and cytoskeletal arrangement. Differentiation involves the coordinated expression of specific genes involved in producing the adipocyte phenotype.³⁷ Transcriptional regulation of adipocyte differentiation during development is largely controlled by peroxisome proliferator-activated receptor- γ (PPAR- γ). PPAR- γ is the factor demonstrated to be the most specific to adipogenic differentiation. When its receptor becomes activated by its agonist ligand in a target cell, a process of differentiation into an adipocyte begins via morphologic changes, lipid accumulation, and activation of genes distinctively expressed by the mature adipocyte. Additional support during differentiation comes from CCAAT/enhancer-binding proteins (C/EBPs), with C/EBP- β and C/EBP- α specifically stimulating PPAR- γ expression during early differentiation and C/EBP- α having a similar role later in the pathway. Recently, lipoprotein lipase (LPL), specific Krüppel-like factors (KLF5, KLF15, and KLF2), early growth response 2 (Krox20), and early B-cell (O/E-1) factors have also been implicated in adipocyte differentiation.^{38–42} Both insulin and insulin-like growth factor-1 (IGF-1) are known to be required for adipocyte differentiation. Simultaneously, preadipocyte factor-1 (pref-1), whose role is in the maintenance of the preadipocyte phenotype, is decreased during adipocyte differentiation. Late markers of differentiation, which are factors produced once adipocytes mature, include adipisin, angiotensinogen II, acyl-coenzyme A (Co-A)-binding protein (ACBP), leptin, and two

fatty acid-binding proteins (FABP) known as adipocyte lipid binding protein (aP2) and keratinocyte lipid-binding protein. As preadipocytes differentiate into adipocytes, they lose their morphologic similarities to fibroblasts via decreased expression of collagen types I and III and increased production of collagen type IV, laminin, entactin, and glycosaminoglycans. In fact, inhibition of collagen synthesis during this phase actually blocks preadipocyte differentiation.⁴³

Biology of ASCs

Preadipocytes were first described in 1976 by Dardick in a rat model;⁴⁴ similar cells were later isolated from human adipose tissues.^{45–47} Isolated preadipocytes were initially used to probe adipocyte biology *in vitro*, leading to the recognition that different anatomic locations and adipose depots express different biological characteristics, such as adipocyte size and lipolytic potential. In 2001, Zuk⁴⁸ first discussed the differentiation plasticity of preadipocytes and eventually the term adipose-derived stem cell (ASC) was adopted to encompass the characteristics of self-renewal, asymmetric division, and multi-lineage potency. Although ASCs proliferate and rapidly expand in culture, exogenous growth factors are required to induce lineage-specific differentiation.⁴⁹ Differentiation of ASCs to other mesenchymal phenotypes has been well established both *in vitro* and *in vivo*. ASC differentiation to cell lineages of the ectodermal and endodermal germ layers has also been successful in several studies.^{50–68}

Adipose-derived stem cells (ASCs) are prevalent within human adipose tissue, surrounding blood vessels and residing within the connective tissue framework. These non-lipid-laden stromal cells are easily isolated from either suction-aspirated adipose tissue or excised human fat via enzymatic collagenase digestion. Numerous descriptions for cell isolation methods appear in the literature.^{69–71} The resultant freshly isolated cell pellet is highly heterogeneous and is named the stromal vascular fraction (SVF). When SVF cells are placed in culture, the ASCs adhere to the surface of an untreated tissue culture flask after 6–8 hours' incubation at 37°C and 5% CO₂. Once ASCs have adhered to the culture flask surface, non-adherent populations, representing approximately 7–15% of the SVF and consisting of mainly hematopoietic origin cells, are washed away with sterile phosphate buffered solution and/or fresh culture media. A commonly used ASC expansion medium consists of a Dulbecco's Modified Eagle Medium (DMEM) and DMEM/F12 media combination, with 10% serum, antibiotic (e.g., penicillin, streptomycin), and a small amount of dexamethasone to halt differentiation to another mesenchymal lineage. Once in culture, specific growth factors or other additives can be applied to direct the differentiation to a specific phenotype, such as adipose, bone, cartilage, or muscle.

SVF is attractive therapeutically because it may be obtained from tissue within 60–90 minutes, and the isolation can be performed in a clean room near an operating room, or even within an operating room using available automated devices. Collagenase digestion results in approximately 2–5 × 10⁵ nucleated SVF cells per gram of adipose tissue. However, complete ASC isolation takes 24 hours and requires access to cell culture facilities. Benefits of cell culture also include the ability to differentially expand the cell number, select for specific subpopulations, or control the microenvironment for

directed differentiation, or seeding of a scaffold material. Flow cytometry characterization of the surface markers on freshly isolated and cultured adipose-derived cells can be performed, and shows the presence of early progenitor markers such as CD34 and CD90.^{49,72}

Freshly isolated SVF obtained directly from harvested adipose tissue has diverse patterns of cell surface markers as identified by flow cytometry.^{50,72} Zimmerlin and colleagues identified several similar cell surface markers in ASCs compared with bone marrow-derived stem cells (BMSCs).^{72,73} Li and colleagues reported four subpopulations of interest that can be isolated and cultured.⁷⁰ The first subpopulation is CD31+/CD34- and is classified as "mature endothelial" as it expresses the endothelial marker of CD31 but lacks the progenitor marker CD34. The second subpopulation is classified as "endothelial stem" and is CD31+/CD34+, expressing both endothelial and progenitor markers. A third subpopulation, CD31-/CD34+ is classified as "adipose stem" (i.e., ASC), displaying just progenitor markers. The fourth subpopulation represents a "pericyte group" characterized by surface markers CD146+/CD90+/CD31-/CD34-. Pericytes function as contractile cells that regulate blood flow and reside adjacent to the blood vessel walls as shown by immunostaining.⁵¹ Similar to BMSCs, ASCs do not express major histocompatibility complex (MHC)-II and inhibit proliferation of activated peripheral blood mononuclear cells, suggesting a role for modulating the immune system in inflammatory disorders or allogeneic transplantation.⁵⁰ In fact, ASCs are an active target of much research in the area of vascularized composite tissue transplantation, hoping to aid in the induction of tolerance to transplanted allograft tissues.

Nonenzymatic isolation of ASCs and SVF has been a topic of recent interest, driven by a potentially less restrictive regulatory pathway. Strategies have focused on mechanical forces such as ultrasound, but there is no evidence to suggest equivalence to enzymatic digestion. There has also been interest in whether there are viable ASCs in the aqueous portion of the lipoaspirate, obviating the need to expose tissue grafts to digestive enzymes. Although some cells are present, the quantity is insufficient for clinical use. Because the ASCs are firmly embedded within the connective tissue, enzymatic digestion is currently necessary to release them in significant quantity for use in clinical applications.

Fat harvesting, preparation and grafting techniques

Over the last 30 years, numerous fat grafting techniques have been described with each iteration promising improved consistency and more reliable outcomes. To date, a standard has yet to be universally adopted by all authorities. Most variables that remain in question relate to three major steps in fat grafting: (1) harvesting from the donor site, (2) processing the fat *ex vivo*, and (3) reintroduction to the recipient site. Investigators refining the techniques of fat harvesting, preparation, and grafting have relied upon clinical outcomes in addition to utilizing both *in vitro* and *in vivo* models of adipogenesis. Lack of consensus thus far has resulted from numerous studies showing equivocal results when various methodologies are compared. In 2009, the ASPS Fat Graft Task Force published its evidence-based guidelines for autologous fat grafting based upon a thorough review of the existing literature.

Common approaches to fat harvesting include syringe aspiration and liposuction.^{25,74,75} The primary concerns during tissue harvest are minimizing the level of invasiveness (i.e., patient safety) and maximizing tissue viability (i.e., efficacy). The ASPS Fat Graft Task Force in its 2009 report suggested that tissue harvest be performed using a 3- to 4-mm blunt cannula, while utilizing minimal amounts of suction required for tissue extraction.⁷⁶ However, a 2013 report by Lee showed no statistically significant differences in parcel size or histologic architecture when fat was harvested with suction pressures up to -0.83 atm through a standard 4-mm cannula.⁷⁷ Additionally, the utilization of ultrasound-assisted liposuction also appears to have minimal effect on cellular viability and overall graft survival rates, with similar amounts of SVF cell populations present irrespective of the harvest technique utilized.⁷⁸

Once the fat has been harvested, it can be prepared for injection via one of several methods, which can include washing with physiologic buffers, centrifugation (for separation of cells from debris), decantation, or concentration (i.e., rolling across an absorbent medium).^{28,79-83} To avoid contamination and maximize tissue viability, exposure to air and mechanical damage should again be minimized. The ASPS Fat Graft Task Force in its 2009 report suggested that viable adipocytes be separated from blood, serum, and damaged adipocytes via centrifugation (3000 rpm for 3 minutes) while remaining within the harvest syringe to limit exposures.⁷⁶ However, Fisher *et al.* demonstrated superior graft retention rates with gauze-rolled fat, attributed in part to greater retention of the SVF components.⁷⁸ In a 2012 review of fat grafting techniques, Gir and colleagues concluded the body of evidence to date does not support one processing technique above another.⁶ They do, however, caution that when centrifugation is used, several studies suggest that forces greater than 3000 rpm (1200 g) can inflict greater levels of cellular damage that can negatively impact overall graft retention rates.

Once refined, fat is subsequently injected subcutaneously with an assortment of delivery methods using blunt-tipped needles. To optimize fat graft viability, mechanical damage of the tissue must be minimized during the injection process. The ASPS Fat Graft Task Force 2009 report suggests that injection be performed using a 2- to 2.5-mm blunt-tipped infusion cannula (or a similar blunt needle); small aliquots of fat should be deposited serially, with multiple injections occurring in multiple tissue planes within the area of augmentation.⁷⁶ Ozsoy *et al.* compared three different diameters of injection Coleman-type cannulas and found that adipocyte viability was significantly greater with 2.5-mm-diameter injection cannulas compared with smaller diameter cannulas (1.6 or 2 mm).⁸⁴ Adipocytes have been shown to be highly susceptible to the effects of shear stress, which is proportional to flow rate during injection. Lee *et al.* demonstrated that slow injections (0.5–1 cc/second) resulted in a 38% improvement in fat graft survival over fast injections (3–5 cc/second) through similar sized cannulas.⁷⁷ Special consideration should be made to minimize the factors that increase shear stress upon the graft. Variables such as viscosity, concentration, cannula length, cannula diameter, and flow rate play a significant role and can negatively impact fat graft survival to a high degree when proper technique is not utilized.

Another variable to consider in the overall technique of fat grafting is the ideal donor site. When harvests from four

commonly used donor sites (abdominal fat, thigh fat, flank fat, or knee fat) from five subjects were evaluated, no immediate differences in adipocyte viability were observed.⁸⁵ These results were corroborated by another study in which no differences in fat viability were observed when fat was harvested from three donor sites from one subject (thigh, abdomen, and breast) and injected into a nude mouse model.⁸⁶ However, these results were challenged by Schipper *et al.*, showing there is variability in physiologic function of ASCs that have been harvested from different subcutaneous depots, with the superficial abdominal depot being most resilient and providing superior graft retention rates.⁸⁷ Additionally, the authors demonstrated age-related changes in ASC function that may impact overall graft survival irrespective of depot used, stressing the importance of appropriate patient selection. Furthermore, ASC counts in harvested tissues are observed to vary widely from patient to patient and not only from depot to depot.

Published data thus far have failed to produce an agreed-upon algorithm of the required components for successful, consistent, and durable autologous fat transplantation. There is a modest preference in favor of the following approach: harvesting abdominal fat with a blunt-tip cannula technique, centrifugation without washing or other manipulation, and immediate injection of small aliquots of fat by means of multiple passes.⁷ After almost 30 years of varying applications of fat transfer, surgeons and scientists alike are attempting to provide insights into fat grafting techniques so that patients are provided with optimized clinical outcomes. Large, well-designed prospective randomized clinical trials are needed but remain elusive given the sheer number of variables in question and difficulty with appropriately blinding surgeons.

Safety concerns

The overall safety of fat grafting procedures is well established, with low morbidity and relatively few perioperative complications. Overall, patients tolerate the procedure exceedingly well. However, when questions regarding the safety of fat grafting arise, they are generally related to oncologic matters. The presumed interactions of fat grafts with the recipient tissues are of primary concern – either the ability to scar and distort cellular architecture or the ability of progenitor cells to push and/or accelerate aberrant processes. Breast cancer-related defects remain by far the most common oncologic defects reconstructed with autologous fat.⁸⁸ With breast cancer being the most common cancer in females and the leading cause of cancer-related death in females, in 1987 the ASPS banned fat grafting to the breast primarily due to concerns regarding ongoing cancer surveillance. This was presumed to be due to low graft retention rates and high rates of fat necrosis that were believed to interfere with routine cancer surveillance. Concerns were later raised about the interaction of ASCs within the fat graft and residual microscopic disease that may remain following extirpation.

In 2007, the ASPS established its Fat Graft Task Force to re-examine the potential hazards and numerous benefits of fat grafting to the breast. During the 1990s, Coleman had introduced and refined the concept of structural fat grafting, leading to increased retention rates and better understanding of graft predictability. In the decades since, there had also

been significant advances in cancer screening technologies through the development of advanced mammography, MRI, and ultrasound techniques. Given the lack of quality data implicating autologous fat transfer, it is surprising that concerns continue to persist.

Concerns regarding oncologic risk of fat grafting are primarily four-fold: (1) interference with cancer surveillance, (2) growth factor release, (3) stem cell malignant transformation, and (4) enhanced migration and metastases of cancer cells. Despite these concerns, fat grafting has become routine in breast cancer reconstruction. This is due to the ability to reliably transfer autologous tissues without the need for microsurgery, simple outpatient-based procedures, and abundance of donor sites with minimal morbidity. Despite the aforementioned concerns, the number of articles in the literature examining fat grafting has steadily risen since the early 1990s as practitioners continually refine and expand upon the technique and its indications.¹

The concerns related to interference with cancer surveillance have by and large been resolved in the literature, with no studies demonstrating evidence of impediment to breast cancer screening or surveillance in patients undergoing fat grafting procedures. A matched cohort analysis of patients undergoing post-mastectomy breast reconstruction with and without fat grafting as a secondary procedure found the incidence of breast biopsy to clarify abnormal imaging was not significantly higher in the fat-grafted group (17.6% versus 7.8%, $p=0.14$).⁸⁹ In fact, fewer than 10% of imaging studies in the fat-grafted cohort were performed to investigate a clinical or radiographic abnormality occupying the same breast quadrant as prior fat injection. Another study by Rubin *et al.* examined mammograms from patients undergoing either breast fat grafting or breast reduction procedures and found scarring ($p<0.001$) and masses requiring biopsy ($p<0.001$) were significantly higher in the breast reduction cohort.⁹⁰ In addition, BI-RADS scores were noted to be significantly higher for breast reduction patients ($p<0.001$). Finally, a 2015 systematic review of fat grafting to the breast that included 35 studies with 3624 patients found fat necrosis was the most common complication (4.4%), biopsy of a subsequent breast lump was required in 2.7% and an interval mammogram in 11.5% of patients.⁹¹ Meta-analysis of comparative studies showed no significant difference in oncological event rates between fat-grafted and non-fat-grafted groups ($p=0.10$).

Currently, a discrepancy exists in the literature surrounding fat grafting and breast cancer. Basic science studies repeatedly demonstrate a strong interplay between ASCs and cancer cells. However, clinical studies fail to demonstrate any significant detrimental effect with one lone exception. *In vitro* experimental models show ASCs can create an enhanced environment promoting tumorigenesis. And yet recurrence rates amongst patients who have had fat grafting after cancer treatment parallel those who have not. This discrepancy exists in large part due to the use of immortalized breast cancer cell lines (BCCs) used to represent primary or recurrent breast cancer in laboratory studies.

Immortalized cell lines are routinely used as surrogates in the laboratory to probe the biologic behavior of various tissue types. One must recall that BCCs utilized today were isolated decades ago from distant metastases and remain phenotypically different from primary cancer cell lines. Great caution must be exercised when interpreting studies utilizing them as

representatives of primary cancer. However, multiple studies do demonstrate strong interactions between BCCs and ASCs. In a study assessing the role of the PDGF- β signaling pathway in cancer metastasis, conditioned medium from MDA-MB-231 and 4T1 BCCs was shown to serve as an attractant via chemotaxis for ASCs.⁹² In another study, *in vitro* migration of triple-negative MD-MB-231 was enhanced by ASC co-culture; similar results were also achieved with ASC conditioned media.⁹³ In the study, increased metastases were also seen in the liver, lung and spleen in a murine xenograft model, suggesting a role for ASCs in angiogenesis and overall increase in metastatic potential of BCCs. In yet another study, intercellular contact between ASCs and BCCs led to increased expression of malignancy markers in BCCs.⁹⁴ Specifically, ASCs with higher basal levels of hepatocyte growth factor led BCCs in co-culture to increase expression of c-Met, suggesting a role for ASCs in enhancing tumorigenesis. When co-injected with BCCs into nude mice, ASCs were found to differentiate into endothelial-like cells and supported development of larger primary tumors.⁹⁵ CD34+ progenitor cells from fat have been shown to differentiate in endothelial cells and form capillaries that supported tumor growth and metastasis.⁹⁶ Interestingly, ASCs can also promote progression and penetration of the invasive BCC line T4-2, but not its pre-invasive variant HMT-3522-S3, suggesting pre-invasive lesions may not be as sensitive to the local effects of ASCs.⁹⁷ Experimental results like those above should be interpreted with great caution – as the experimental scenarios are highly idealized and do not represent any realistic clinical setting. BCCs again are not representative of clinical malignancies and ASC doses used in the experiments are orders of magnitude higher than could ever be obtained in clinical situations. Nonetheless, caution with cell-enriched therapies is certainly warranted in high-risk patients with breast cancer.

So what exactly is the clinical risk of fat grafting to the breast? Breast cancer recurrence rates are in the range of 5.2–10.6% in patients who have not undergone fat grafting after breast cancer surgery.^{98,99} A systematic review examining the oncologic safety of breast fat grafting reviewed 16 clinical studies including 2100 patients and found a local recurrence rate of 2.2% following fat grafting procedures.¹⁰⁰ A case-control study assessing the oncologic safety of fat grafting reported no significant excess oncologic events in patients after fat grafting with respect to local recurrence (0.95% vs 1.90%, $p=0.33$), regional recurrence (0.95% vs 0%, $p=0.16$), and distant recurrence (3.32% vs 2.61%, $p=0.65$).¹⁰¹ A concurrent systematic review of the literature in the same study identified 1573 women who had fat grafting after oncologic breast surgery and found a loco-regional relapse rate of 2.92% (or 0.95% per year). Another systematic review of the literature included 35 studies and 3624 patients and found a 4.4% weighted mean recurrence rate at 24.6 months amongst patients who underwent autologous fat grafting of the breast.⁹¹ Meta-analysis in that same study showed no significant difference in oncologic event rate between fat-grafted and non-fat-grafted groups. A matched-cohort study assessing loco-regional risk after fat grafting in 321 breast cancer patients and 642 matched controls found no difference in recurrence between fat grafting and control groups ($p=0.792$).¹⁰² However, when cases were limited to intraepithelial neoplasia ($n=37$), fat grafting may have caused 4 recurrence events ($p<0.001$). A subsequent study by the same authors, which looked specifically at 59 patients

with intraepithelial neoplasia compared to 118 matched controls, showed the 5-year local recurrence was 18% versus 3% for fat grafting and controls, respectively ($p=0.02$).¹⁰³

Many systematic reviews/meta-analyses demonstrate similar loco-regional recurrence rates for breast cancer patients who underwent fat grafting relative to control subjects. Yet one case series and one clinical study (both from the same group of authors) point to higher local breast cancer recurrence after fat grafting in patients with intraepithelial neoplasia. In a 2015 review, the authors of the two studies in question showing increased rates of recurrence state that definitive conclusions require large series, controls with matching cancer criteria, and minimum 5-year follow-up.¹⁰⁴ However, the oncologic safety of fat grafting has already been proven in the literature and overwhelmingly demonstrates the overall safety of fat grafting procedures in breast cancer patients.

Diagnosis/patient presentation

While the aesthetic applications of fat grafting have long been described, this technique has numerous reconstructive applications. These include congenital deformities such as hemifacial microsomia and Treacher Collins syndrome. In addition, patients who have sustained previous trauma resulting in significant scarring or tissue loss can often benefit from fat grafting.¹⁰⁵ Patients who have undergone previous cosmetic surgery can also present with iatrogenic deformities such as hollowed upper eyelids, flattening of the posterior jaw line, or contour deformities resulting from liposuction. These areas can be restored to a more youthful and natural appearance with thoughtful and sensible applications of fat grafting.

A newer use of fat appears to come from its regenerative properties on damaged tissues. Rigotti has grafted fat beneath tissue ulcerations in the breast that occurred after radiation therapy, and has noted remarkable restoration and healing of the involved tissues.¹⁰⁶ Irradiated tissue that is stiff and non-compliant can be restored to a more normal consistency and texture and allows filling of contour deformities. In addition, anecdotal reports have been made regarding the improvement of the appearance of scars and skin quality after fat grafting.^{5,105} Amputees with poorly fitting prosthetics also appear to gain benefit from remodeling of the stump at the prosthetic interface, providing more robust tissue coverage and a better, more durable fit.¹⁰⁷

Patient selection

Patient selection must begin with a detailed history, noting pertinent medical comorbidities that may limit therapeutic potential. Candidates must be able to withstand the anesthetic requirements of the procedure, and as a result it may not always be prudent to offer fat grafting to those with profound systemic ailments. Fat grafting to small areas can certainly be performed under local anesthesia, but anything involving more than a few milliliters will generally require sedation at a minimum. Physical examination entails a thorough assessment of the defect in question in addition to assessment of potential donor sites. This allows the physician to formulate a plan for correction of the defect in question. Patients with unrealistic expectations are not good candidates for this or

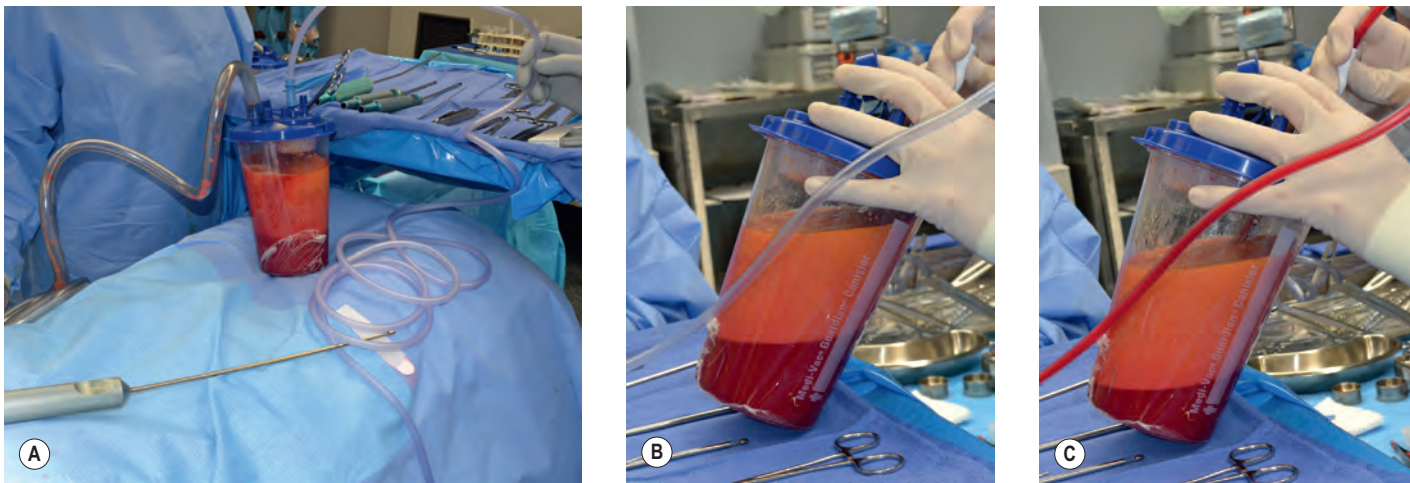


Fig. 20.1 Large volume fat harvest and processing represents a logistical challenge in the operating room. A simple apparatus consists of a sterile collection chamber set up in-line on the sterile field. Machine-generated suction from a standard liposuction aspirator is applied through the system, and a standard liposuction cannula of 3 or 4 mm diameter used to harvest fat into the vessel (A). The aspirate is allowed to decant until the fat separates from the aqueous layer. The aqueous layer is then removed by aspiration with a suction cannula (B,C). Commercially available vessels for large-volume fat collection are also constructed with spigots at the base to drain the aqueous layer.

any other procedure. Patients must be informed that several rounds of fat grafting may be needed to achieve the desired results.

A relative contraindication is the thin patient who does not have sufficient fat stores from which to harvest fat. Since large volumes of fat are generally not needed for the face, enough fat can usually be harvested for these procedures. For fat grafting to the breasts or body, significantly more fat is generally required; often there is a limit to the correction that can be made given the paucity of fat in some patients. Asking the patient to gain weight prior to the procedure is feasible only if the patient is willing and able to maintain that weight afterwards. Weight loss following fat grafting can lead to loss of volume and failure to maintain adequate correction.

Treatment/surgical technique

The surgeon must be familiar with the potential levels of placement (e.g., subdermal, intramuscular, and supraperiosteal) and the amounts necessary at each level to accomplish a desirable change. These amounts will vary across regions of body as well as from patient to patient. Determining the amounts of fat to place and the levels in which to place the fat in order to create subtle, lasting contour changes requires a sophisticated surgical plan.

The Coleman method of fat grafting remains essentially unchanged since the original inception almost three decades ago.²⁴ The process relies upon harvesting the fat gently to preserve its architecture, refining the fat with centrifugation to remove nonviable components and provide a predictable volume, and placement of the fat in small aliquots to increase the surface area and ensure a robust blood supply to the grafted tissue.²³ When these principles are adhered to, fat grafting can be a reproducible and safe procedure. Histologic studies have shown that this method of harvesting and refinement with centrifugation yields fat with a high percentage of survival and near-normal adipose cellular enzyme activity¹⁰⁸ and, for small volume grafting, filtering the fat on sterile

gauze (Telfa rolling) can result in even higher rates of retention of injected fat. However, this method lacks efficiency. In the case of large volume fat injection, the principles of harvest and injection must be adapted to enable greater volumes of fat to be handled efficiently in the operating room (Figs. 20.1–20.6).

Harvesting

As no conclusive differences in viability or graft take have been demonstrated from one site to another in scientific studies, the choice of donor site for fat grafting is dependent on the desires of the patient and accessibility of the fat. In general, the abdomen, “love handle”, posterior hip, back, and lateral thighs are useful sites. In thinner patients, especially males, the medial thighs are an often overlooked but fruitful depot. Incisions should be hidden in creases, scars, stretch marks, or hair-bearing areas, if at all possible. Through these incisions, local anesthetic solution is infiltrated using a blunt



Fig. 20.2 An alternative to decanting the fat is to filter the fat in a medical grade sterile sieve.

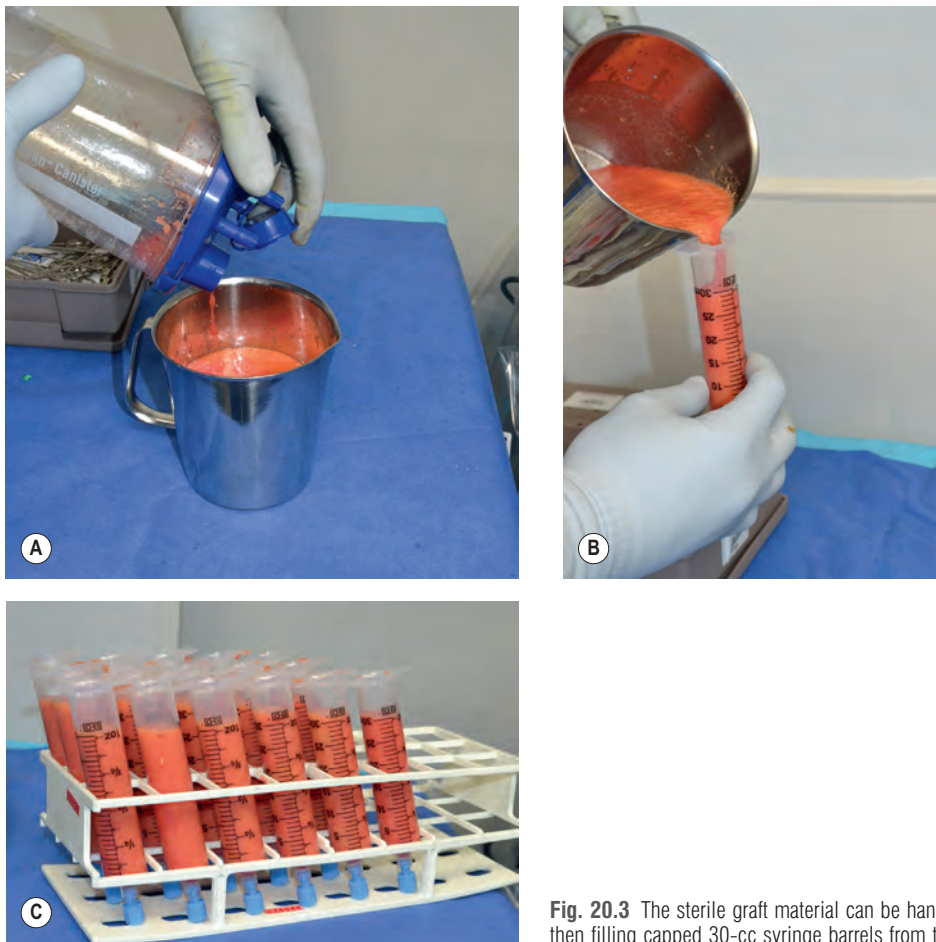


Fig. 20.3 The sterile graft material can be handled by placing it in a vessel with a pour-spout (A), and then filling capped 30-cc syringe barrels from the back (B,C).

infiltration cannula. The local anesthetic mixture should consist of 0.2% lidocaine with 1:200 000 epinephrine. In general, the amount of solution infiltrated is equal to the amount of fat removed (1:1 ratio, superwet technique).

After waiting approximately 10 minutes for the local anesthetic solution to take effect, fat is then harvested using a bucket-handle harvesting cannula. This harvesting cannula is designed to harvest intact fatty tissue parcels that are large

enough to survive, but small enough to pass through the standard 17-gauge infiltration cannula used for grafting. The cannula may be utilized with any vacuum- or power-assisted liposuction equipment or simply attached to 10-ml syringes. If 10-ml syringes are used, the plunger is pulled back only a few milliliters so as not to create too much negative pressure and traumatize the aspirate. Incisions are closed with interrupted 5-0 fast-absorbing sutures.

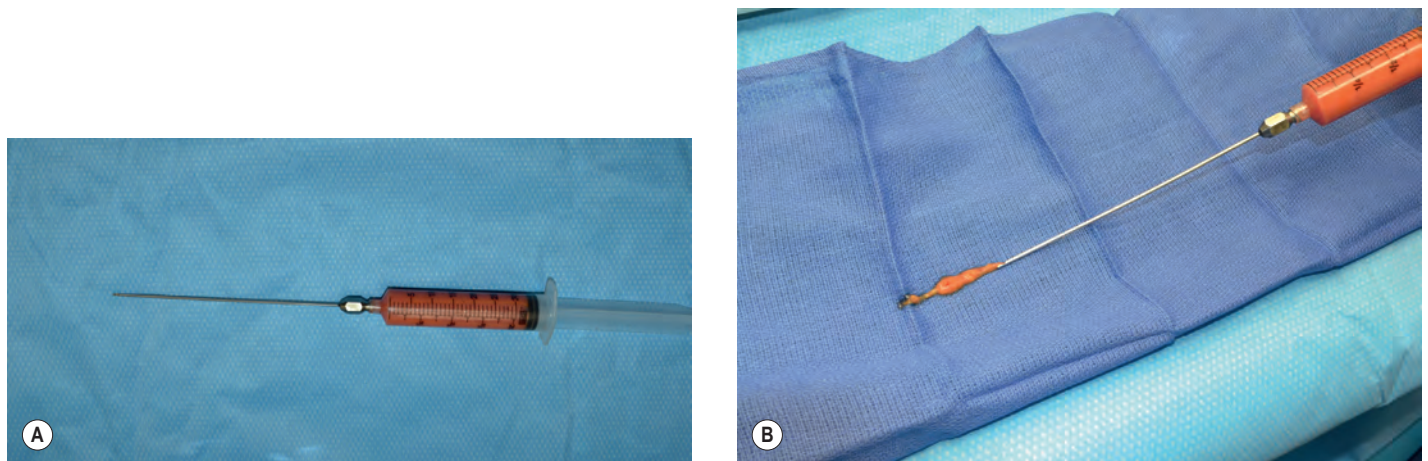


Fig. 20.4 For large-volume fat grafting, a 16-gauge blunt-tipped cannula can be used with the 30-cc syringes (A), and the fat should be easily flowable (B).

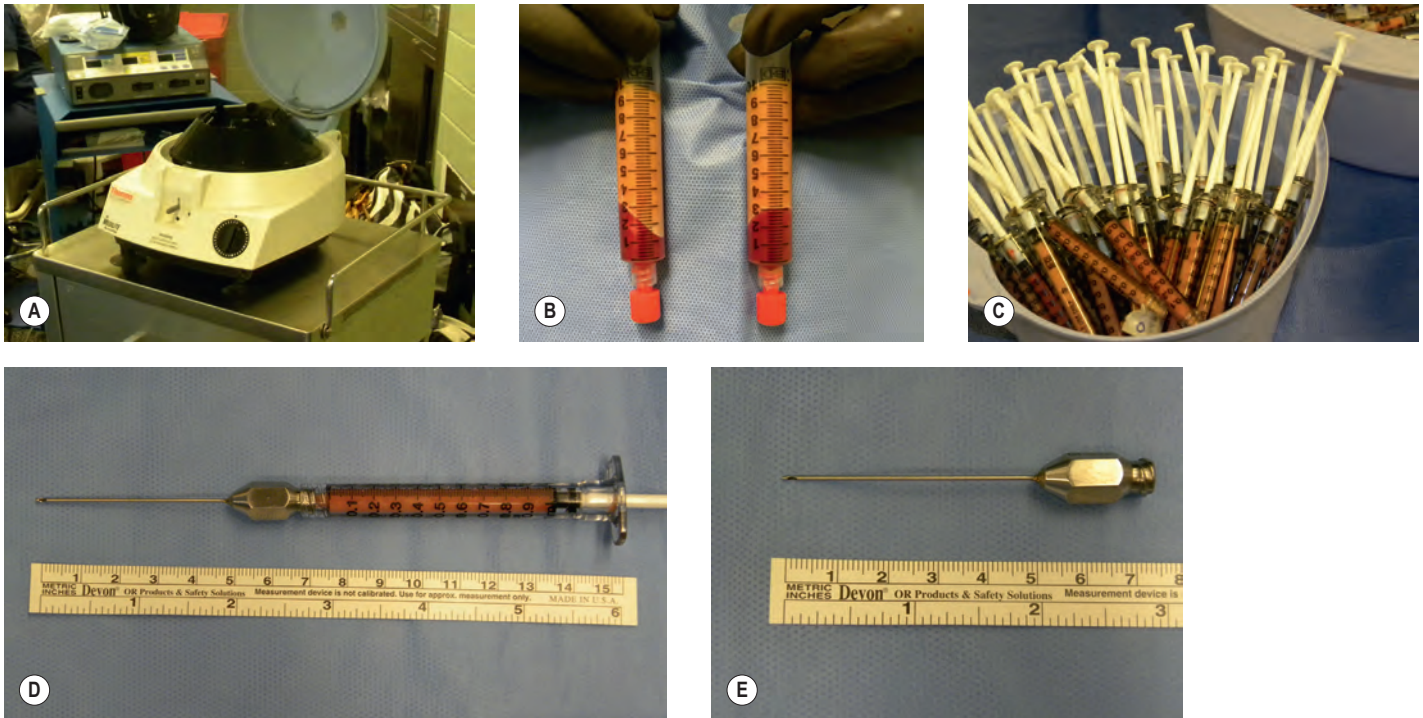


Fig. 20.5 For small-volume fat grafting, the Coleman processing method is highly efficient and reproducible. A tabletop centrifuge (A) with a sterile rotor and tubes, holds 10-cc syringes (B) and generates 1200 G-force at 3000 rpm. The fat is centrifuged for three minutes to separate the oil, fat, and aqueous layers. After draining the aqueous layer and wicking the oil with cotton gauze, the fat can be filled into 1-cc syringes (C), using a Luer connector or by filling the syringe from the back. Blunt-tipped cannulas with a very small aperture and diameter are fitted to the 1-cc syringes for precise placement of fat in the regions such as the face or hand (D,E). These blunt-tipped cannulas also come in curved shapes for accessing tight spaces.

Refinement

As fat is harvested, the first few passes of the cannula will retrieve more local anesthetic than subsequent passes. As suctioning continues, the later passes may contain less aspirate and more blood. After harvest, lipoaspirate is transferred to 10-ml syringes; a Luer-Lok™ plug is used to cap the syringe. Using 10-ml syringes for aspiration avoids the need to transfer. The plunger is removed, and the syringe is placed into a sterile centrifuge. It is vitally important to maintain

sterility during the centrifugation process – a centrifuge with a sterile central rotor and/or sterile sleeves is essential. Centrifugation at 3000 rpm (1200 g) for 3 min concentrates the fat so that the aqueous components (the local anesthetic and blood) can be removed and discarded by releasing the Luer-Lok™ plug. In addition, any oil can be decanted off the top and/or wicked away with gauze pads. The processed fat is then transferred to a 1-cc syringe for placement into the defect.

Placement

Planned incision sites are anesthetized with 0.5% lidocaine with 1:200 000 epinephrine and small stab incisions are made for the placement of fat through 17-gauge Coleman injection cannulas. This not only helps to reduce bruising, but also decreases the chance of accidental intravascular embolization of the fat. The success of the fat grafting procedure depends not only on the harvesting and refinement, but also on the placement of the fat in a manner that increases its chance for optimal survival. This means maximizing the contact surface area of the fatty parcel with the surrounding tissue, such that a blood supply can be conferred to the newly grafted fat. Transferring large globules of fat can result in central necrosis of the mass with subsequent resorption and loss of volume, or possibly even cyst formation.

The fat is gently placed during the withdrawal of a blunt Coleman infiltration cannula. Recall fat can be placed at different levels to accomplish different effects – determining where and at what level to place fat relies upon the skill and experience of the surgeon. For instance, grafting fat



Fig. 20.6 For processing very small volumes for grafting, an easy method is filtering the fat graft on Telfa non-adherent gauze. This method yields a high retention rate, but lacks efficiency.

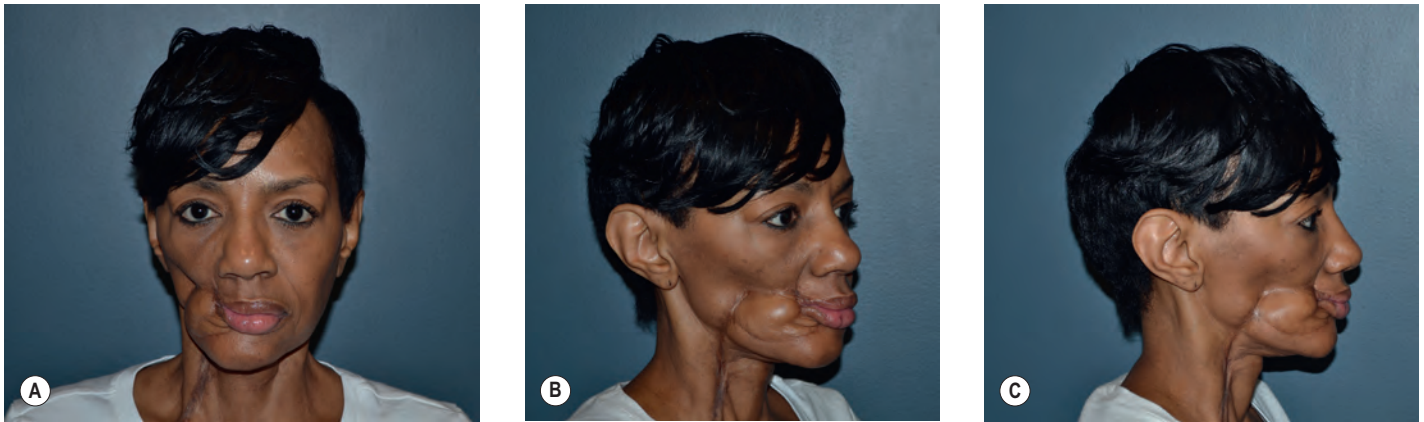


Fig. 20.7 Head and neck cancer reconstruction using fat graft. This 57-year-old woman was treated for an aggressive squamous cell carcinoma with full-thickness cheek resection and reconstruction with a radial forearm free flap and subsequent radiation therapy. She presented three years after her cancer reconstruction, disease free, desiring further reconstruction, this time with fat grafting.

immediately beneath the dermis can improve the quality of the skin, decrease wrinkling, decrease pore size, and may even reduce scarring. Special care must be taken, however, when placing fat superficially, as surface irregularities are more apt to be apparent. This is especially true in areas that have thin skin, such as the lower eyelid. To make changes in the shape of the body that relate to the underlying bony skeleton, fat can be placed above the periosteum. To build bulk, the fat can be placed intramuscularly. The structure should be purposefully built up with tiny aliquots of fat rather

than attempting to insert larger aliquots and then mold the tissue after it is placed. Molding may displace the fat or cause necrosis of some or all of the fat in an area, decreasing predictability and increasing uneven contours. The only time molding should be considered is if an irregularity is noted at the time of placement, as the surface must be smooth before leaving the operating room. The stab incisions used for placement of the fat can be closed with single interrupted 5-0 fast-absorbing sutures. An example of small volume grafting to the face for reconstruction is shown in Figs. 20.7–20.10. Large-volume



Fig. 20.8 Intraoperative markings.

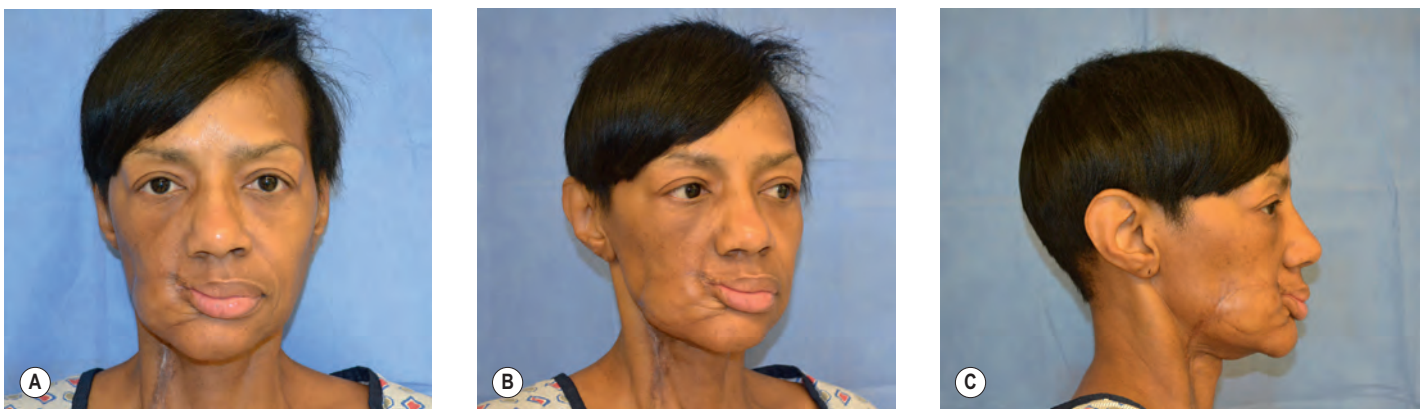


Fig. 20.9 Postoperative results six months after first-stage treatment.

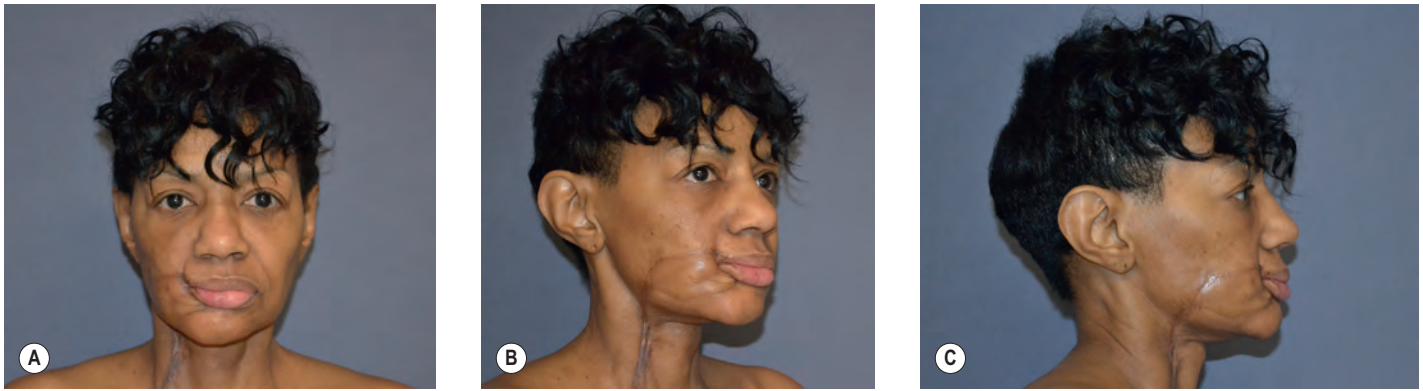


Fig. 20.10 Results eight months after second round of fat grafting. All fat grafting procedures were done on an outpatient basis.

fat grafting to the breast is shown for lumpectomy defects (Fig. 20.11), replacement of implants (Figs. 20.12–20.14), and total breast reconstruction (Fig. 20.15).

Postoperative care

Care of the patient after fat grafting remains relatively simple. Grafted areas are not routinely dressed, and patients may shower 48 hours following the procedure. If possible, grafted

areas should remain elevated above the level of the heart for 72 hours following the procedure. Direct pressure upon the grafted area should be avoided for one week. Sutures in the face are removed in 4–5 days, and resorbable sutures at other sites can be removed in one week or left to dissolve away on their own. Donor sites may be dressed with compression garments or an abdominal binder if large volumes are harvested. Deep massage is avoided for one month postoperatively. Preoperative antibiotics will suffice for most patients, while those patients that are at high risk for surgical site infection can be given 3–5 days of antibiotics postoperatively.

Outcomes, prognosis, and complications

Fat grafting procedures by and large are deemed to be low risk and are associated with low perioperative morbidity rates given proper patient selection. Soreness and swelling are common, but not every patient will experience them. The most significant risk remains the unpredictable nature of the graft, where the recipient site may simply reabsorb most of the transferred fat. The extent of resorption at this time cannot be predicted for a given individual, but some degree of resorption will happen in every patient. Rare but possible fat transfer risks and complications include: allergic reaction to the local anesthetic, permanent discoloration caused by a ruptured blood vessel, fat necrosis, oil cyst formation, calcification, overcorrection, perioperative bleeding, a blood clot at the treatment or donor site, a blood-borne infection (more likely if combined with another cosmetic procedure), scarring, and a fat embolism from direct fat injection into a blood vessel. Most problematic is the high potential for contour irregularities visible through the skin, which can occur in both the recipient and donor sites. In the recipient sites, excess grafted fat will appear as lumps beneath the skin, and is generally the result of placement of a volume that was too large just beneath thin skin. Unwanted parcels of fat can be difficult to remove at a later time, therefore prudence should be exercised when placing grafts. Potential remedies for irregularities caused by excess fat include liposuctioning of the fat, direct excision, lipodissolve products (not approved by the FDA in the United States), and potentially off-label use of the deoxycholic acid derivative ATX-101 (known as Kybella®).^{109–111}

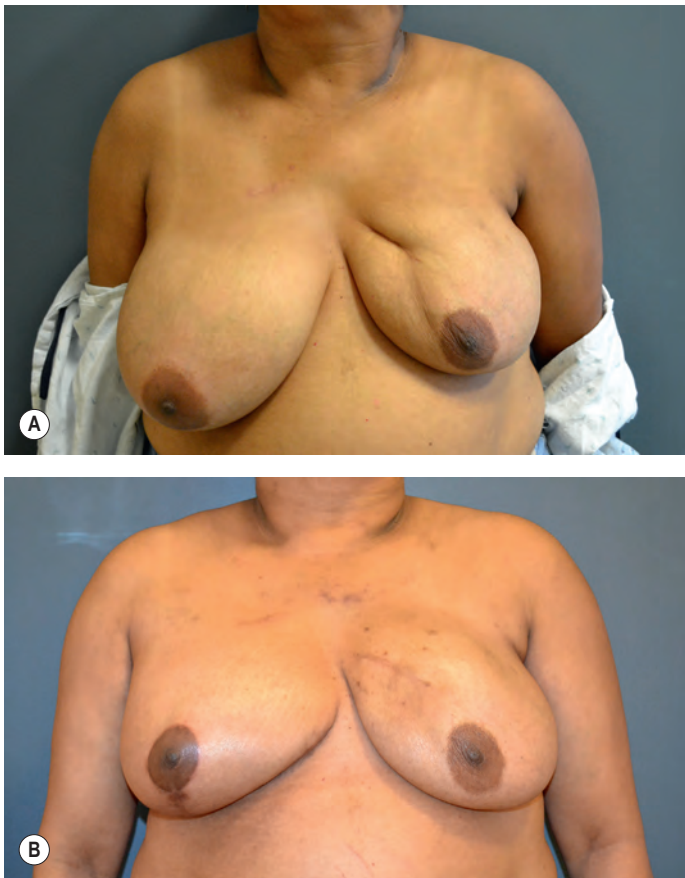


Fig. 20.11 54-year-old woman three years status post left breast quadrantectomy and radiation therapy for invasive breast carcinoma (A). Patient shown five months status post fat grafting with scar release of the left breast, and concurrent reduction of right breast for symmetry (B).

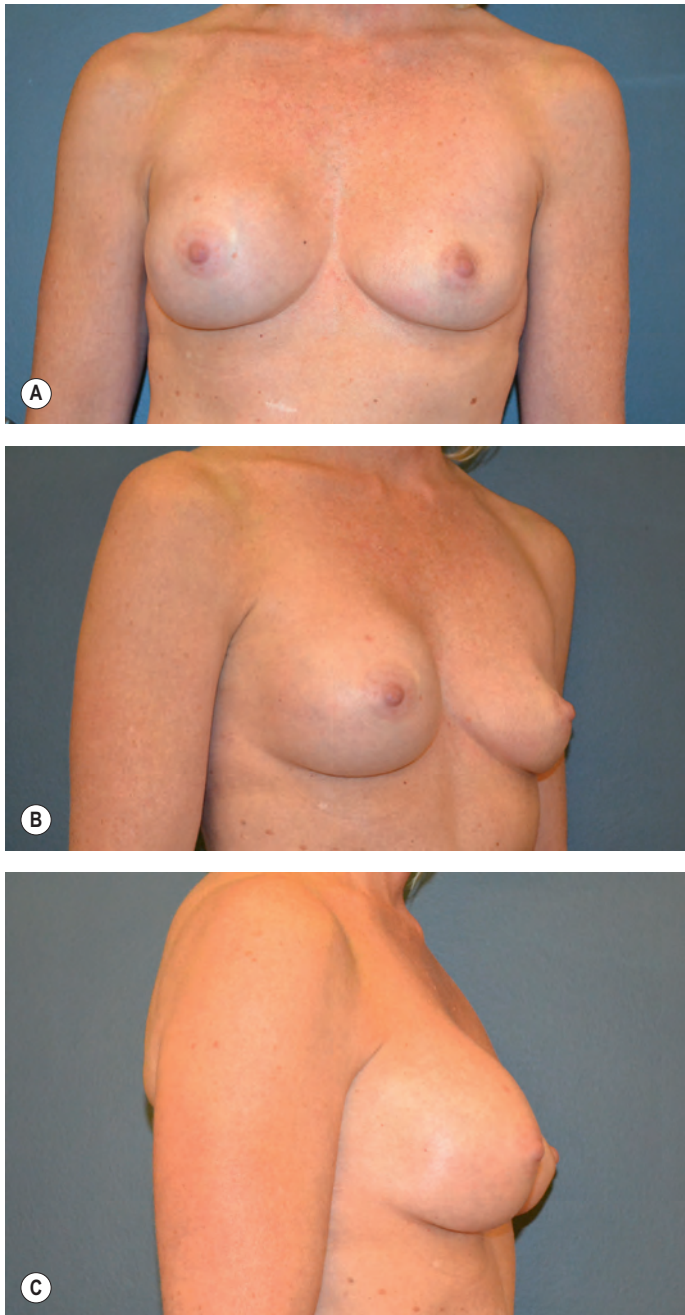


Fig. 20.12 Removal of breast implants and replacement with fat graft in the same procedure. This 48-year-old woman had severe right breast capsular contracture with pain. This was a recurrent problem for this patient. She presented for explantation of the implants.

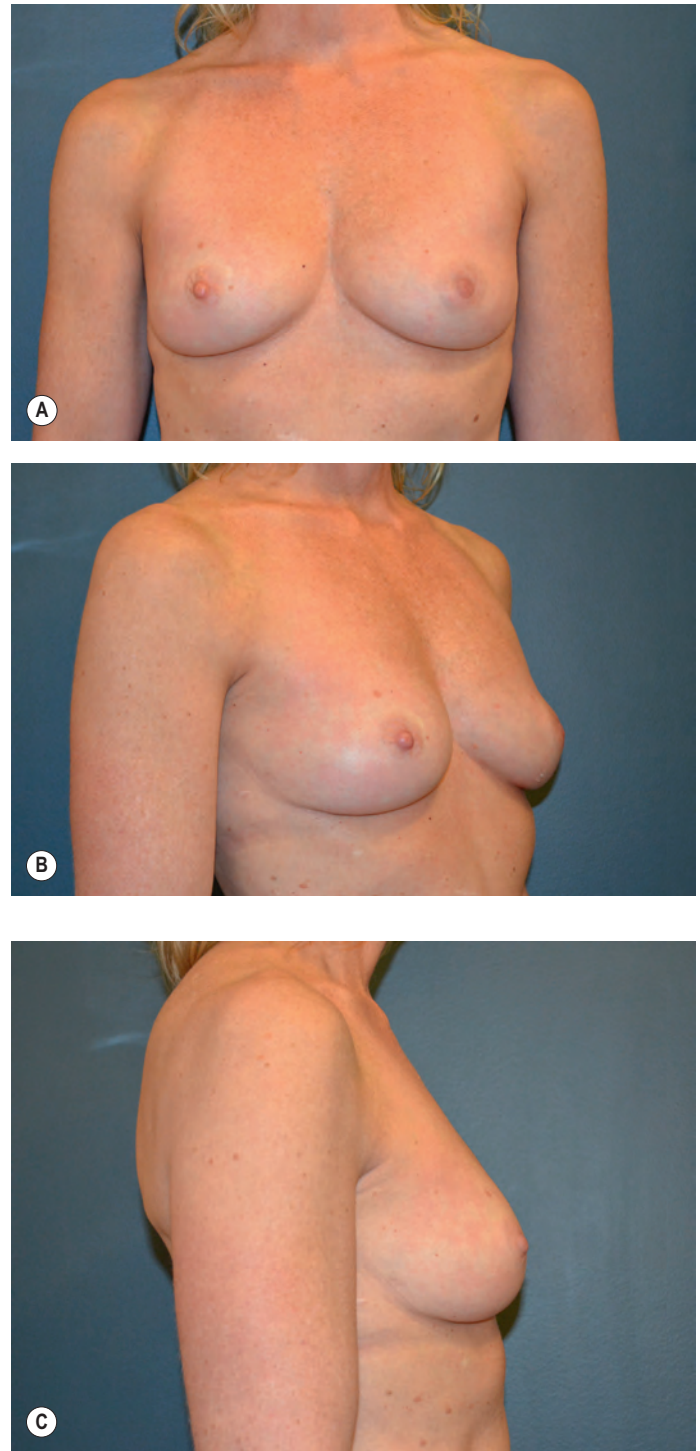


Fig. 20.13 Patient six months after removal of 350-cc smooth round saline implants and simultaneous grafting of 380 cc of fat per breast.



Fig. 20.14 The same patient shown 18 months after single-stage fat grafting.



Fig. 20.15 (A) 45-year-old woman status post bilateral mastectomies. She has not been treated with radiation. (B) Patient is shown three years after breast reconstruction with external expansion (BRAVA), and three fat grafting treatments. (Case courtesy of Dr. Roger Khouri.)

Irregularities in the donor sites can be pronounced, particularly if too much fat is removed from a single area. Significant changes in weight can also result in related changes in the size of the area grafted, therefore patients are encouraged to have fat grafting procedures performed when they are at their ideal body weight and to maintain that weight indefinitely.

Secondary procedures

With fat grafting, secondary procedures, or touch-up procedures, are possible if an incorrect volume of fat was placed initially. Infiltration and swelling at the time of surgery, in addition to the unpredictable resorption of fat, make

achieving perfection in a single stage difficult. Patients should be instructed that multiple rounds of grafting might be required to achieve the desired end. In reconstructive cases, the soft tissue envelope often limits the surgeon, and as tissue quality improves after initial fat grafting, the area may become more receptive to larger subsequent volumes. It is far better to under-correct a deficient area and return to the operating room for a second stage, if necessary, at a later date. In complicated liposuction cases, a second stage is often part of the original plan, as it can be very difficult to make an area perfect in one procedure. Generally, the goal of the first procedure is to fill in large defects with significant amounts of fat and later to come back and refine the area with additional grafts.



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Vascular territories

Steven F. Morris and G. Ian Taylor

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SYNOPSIS

- This chapter provides an overview of the angiosome concept and reviews the vascular anatomy of the body. The historical perspective summarizes the major progress in understanding the vascular basis and clinical applications of flaps in reconstructive surgery.
- The anatomical basis of angiosomes, choke anastomotic vessels, arterial territories, and venous drainage of the human body are summarized. The neurovascular territories of skin and muscle are described. Comparisons with other species highlights the consistent features of vascular anatomy of the human body and illustrates the need to be aware of the vascular anatomy of animal flap models.
- The vascular anatomy of skin, muscle, and bone of each region of the body is discussed with an emphasis on flap design, avoiding surgical complications and providing an overview of angiosomes of the body.
- The general concepts of the vascular supply to tissues of the body are reviewed. The importance of these concepts to flap design is highlighted with clinical examples. These concepts also provide the basis for interpreting physiologic and pathologic events in skin flaps.
- The overall architecture of the vasculature of the human body is consistent but there is significant variability in individual perforator anatomy. Therefore, a versatile operative plan is needed for successful flap design.
- Methods of preoperative assessment of vascular anatomy and types of flaps, including skin, fasciocutaneous, musculocutaneous and perforator flaps, are reviewed.
- The anatomic basis of the delay phenomenon and procedure is explored.

Introduction

The angiosome theory has become well accepted in the field of plastic and reconstructive surgery and allows the conceptualization of the vascular supply to all tissues of the human body. An angiosome is a composite block of tissue supplied

by a main source vessel. The adjacent angiosomes are linked either by reduced-caliber choke anastomotic vessels or vessels without reduction in caliber – the true anastomoses of adjacent arterioles. The latter are seen in many muscles or in the skin, especially where vessels accompany cutaneous nerves. Flaps designed along an axis of vessels linked by true anastomoses have a longer survival length similar to a flap that has been delayed. The anastomotic arteries are matched by veins devoid of valves that allow bidirectional flow. The entire human body consists of innumerable arcades of interconnecting vessels which supply all tissues.

In 1977, Converse¹ stated that “there is no simple and all-encompassing system which is suitable for classifying skin flaps”. It is now generally agreed that the anatomical vascular basis of the flap provides the most accurate approach for classification. Specific, anatomically based nomenclature simplifies communication between surgeons and allows for the advancement of the field of plastic and reconstructive surgery. The main named source vessels throughout the body provide a useful road map for the description of flaps.

The vascular architecture of the body is arranged anatomically as a continuous series of vascular loops, like the tiers of a Roman aqueduct, that increase in number while their size and caliber decrease as they approach the capillary bed (Fig. 21.1). The reverse situation occurs on the venous side. This anatomic arrangement of the vascular “skeleton” is shown beautifully in the corrosion cast studies of newborn babies performed by Tompsett² that reside in the Hunterian Museum at the Royal College of Surgeons in London (Fig. 21.2). Note how the main arterial loops hug the bony framework and the secondary arcades follow the intermuscular and intramuscular connective tissue framework. The “keystones” of these arcades are represented usually by reduced-caliber (choke anastomotic) arteries and arterioles, matched on the venous side by avalvular (oscillating) veins that permit bidirectional flow. Choke arteries and avalvular veins have an essential role in controlling this pressure gradient across the capillary bed (see Fig. 21.1).

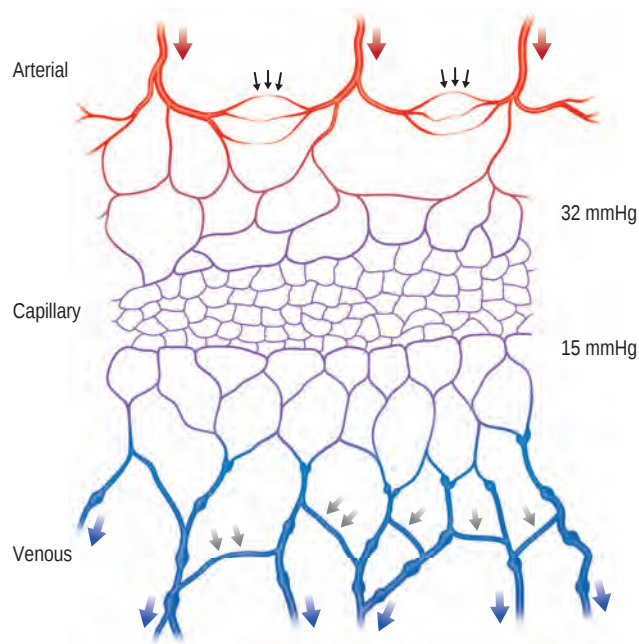


Fig. 21.1 Schematic representation of the arterial supply and venous drainage of the capillary bed. Note the choke arteries (small black arrows) and bidirectional avalvular veins (small shaded arrows) that allow equilibration of flow and pressure to the capillary bed from arterioles (red arrows) and from the capillary bed through venules (blue arrows).

Access the Historical Perspective section, including Figs. 21.3 and 21.4, online at

<http://www.expertconsult.com>

Vascular anatomical research

Angiosome

The angiosome (from the Greek *angeion*, meaning vessel, and *somite*, meaning segment or sector of the body derived from *soma*, body) is defined as a composite block of tissue supplied by a main source artery. The source arteries (segmental or distributing arteries) that supply these blocks of tissue are responsible for the supply of the skin and the underlying deep structures. When pieced together like a jigsaw puzzle, they constitute the three-dimensional vascular territories of the body. In this section we present the basis of the anatomical studies which are the foundation of the angiosome concept.

The angiographic studies produced by Salmon using lead oxide, gelatin, and water were exceptional; however, modifications of the technique have further improved results.^{41,42} In particular, reducing the concentration of lead oxide has improved computed tomographic (CT) angiographic anatomic studies.⁴³ A review of vascular injection techniques reveals the wide array of techniques available for investigation.⁴⁴

Initially, cadaver injection studies to study the vascular anatomy of the human integument and other structures utilized intra-arterial injections of radiopaque substances such as barium sulfate or lead oxide or visible substances such as

latex and ink. Depending on the specific study, the area of tissue of interest was then dissected and radiographed. As the radiographic film quality improved, the quality of the image of the small blood vessels improved. However, studies using simple radiographs have largely been replaced by CT techniques.^{43,45,46} These investigations were conducted in fresh cadavers. In the majority of studies, the anatomical question was problem-oriented in a desire to provide a surgical solution to the individual patient's needs. We have performed a large number of fresh cadaver studies, investigating various regions, tissues, and combinations of tissues. This has included an investigation of the entire integument and underlying deep structures in a series of total body studies of the arteries,⁴⁷ which led to the angiosome concept, discussed in detail in a later section. This was followed by studies of the veins⁴⁸ and the neurovascular territories of the body⁴⁹ and detailed studies of the angiosomes of the forearm,⁵⁰ the leg,⁵¹ and the head and neck,⁵² as well as a comparative study of a series of mammals.⁵³ As well, we have performed detailed analyses of numerous muscle flaps including sartorius,⁵⁴ rectus femoris,⁵⁵ gracilis,⁵⁶ pectoralis major,⁵⁷ and skin flaps, including the reversed sural artery flap,⁵⁸ thoracodorsal artery perforator

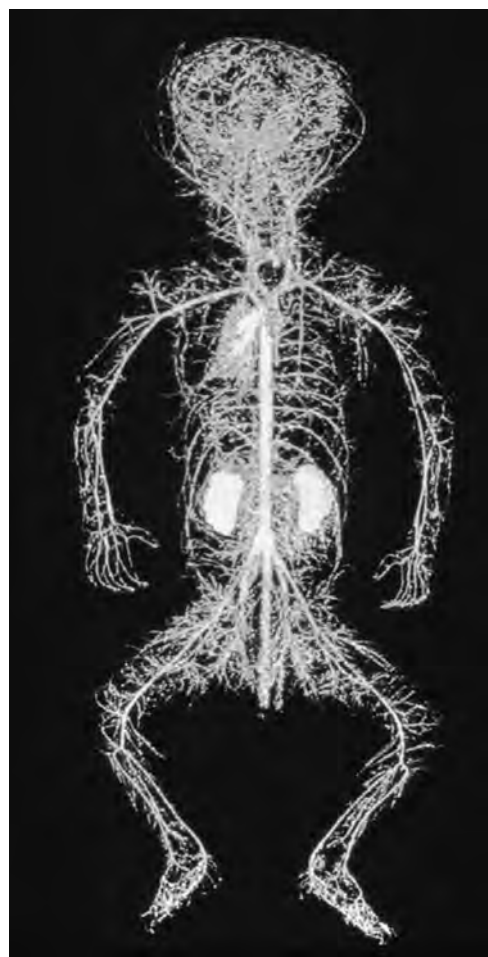


Fig. 21.2 Tompsett's arterial skeleton of the body. This corrosion cast of the newborn body shows the arterial architecture of the body. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

Historical perspective

Plastic surgery evolved as a specialty in Europe and North America to restore the mutilated victims of the two World Wars. With artistic flair and geometric precision, tissues were advanced and rotated. These random flaps were transposed locally and dispatched to distant sites on limb carriers, only to be rebuffed on occasion by necrosis. Gillies often lamented that “plastic surgery is a constant battle between blood supply and beauty”.³ Gradually, rigid length-to-breadth flap ratios were calculated for different regions of the body because most of the flaps were designed without a precise knowledge or appreciation of the vascular supply of flaps. The flaps designed were “random” since it was not appreciated that the vascular supply was crucial to flap survival and there was little understanding of the anatomy of the underlying vasculature.

Unfortunately, this anatomic information was available but overlooked. In 1889, Manchot⁴ performed the first examination of the vascular supply of the human integument. His treatise, *Die Hautarterien des menschlichen Körpers* [*The Cutaneous Arteries of the Human Body*], was initially published in German and later translated to English.⁵ Manchot identified the cutaneous perforators, assigned them to their underlying source vessels, and charted the cutaneous vascular territories of the body (Fig. 21.3). He did not have the advantage of radiography since Röntgen was not to make his discovery until several years later. Nevertheless, the accuracy of Manchot's work has mostly stood the test of time.

In 1893, Spalteholz⁶ published an important paper on the origin, course, and distribution of the cutaneous perforators in adult and neonatal cadavers. He performed arterial injections of gelatin and various pigments. The soft tissues were fixed in alcohol and subtracted in xylol, and the resulting vascular network was embedded in Canada Balsam. Spalteholz's main study concentrated on the detailed circulation of the skin. He made an important distinction between direct cutaneous vessels, which supply the skin, and indirect cutaneous vessels, which are terminal branches of vessels supplying the deeper organs, especially the muscles. A detailed account of this work was published by Timmons⁷ in a review of the landmarks in the anatomic study of the skin's blood supply.

The next major study was performed by Salmon,^{8,9} a French anatomist and surgeon in the 1930s. Manchot had defined approximately 40 cutaneous territories that excluded the head, neck, hands, and feet. Salmon knew of Manchot's studies and set out to reappraise his work. Aided by radiography, he was able to delineate the smaller vessels of the cutaneous circulation and charted more than 80 territories encompassing the entire body (Fig. 21.4). Salmon noted the interconnections that exist between perforators, and his observation of the density and size of the vessels in different regions of the body led him to define what he called the hypervascular and hypovascular zones. His work has become available in English.¹⁰ Ironically, in the preface to Michel Salmon's book on the cutaneous vascular anatomy published originally in 1936,⁸ Raymond Grégoire stated: “This new work by Michel Salmon is a painstaking study that no surgeon from now on can ignore and few anatomists would have had the courage to undertake.” Indeed, if we had heeded this advice, plastic surgery would have evolved much earlier!

In 1975, Schafer¹¹ published an important study on the arterial and venous anatomy of the lower extremity. Scribtor and an ink-serum mixture were injected into the lower limbs of adults and into the entire circulation of fetal and neonatal cadavers. Schafer concluded that most cutaneous arteries emerge in rows from the intermuscular septa or occasionally from the intramuscular septa. In addition, he highlighted the two systems of perforating veins: the venae communicantes, large veins that pierce the deep fascia and connect the superficial venous plexus to the deep venous system; and the venae comitantes, small, usually paired veins that accompany the cutaneous arterial perforators.

Early last century, advances on the clinical front gave significance to the work of these great anatomists. In 1906, Tansini¹² reported a latissimus dorsi flap supplied by the thoracodorsal artery. In 1919, Davis¹³ published *Plastic Surgery* and introduced many of the chapters with illustrations from Manchot's book. In 1921, Blair¹⁴ described a forehead flap based on the superficial temporal vessels, and in 1929, Esser published *Artery Flaps*.¹⁵ In 1937, Webster¹⁶ again cited the work of Manchot when he described a long, bipedicle thoracoepigastric flap based on named arteries that extended from the groin to the axilla. Shaw and Payne¹⁷ used the clinical information available in wartime to provide one-stage direct flaps for hand reconstruction. In 1965, Bakamjian¹⁸ drew attention to the long paramedian perforators of the internal thoracic system.

The 1970s witnessed the beginning of the “anatomic revolution”. McGregor and Morgan¹⁹ differentiated between large flaps based on a known axial blood supply and those based on random vessels. Daniel and Williams²⁰ reappraised the work of Manchot and others and classified the cutaneous arteries into direct cutaneous and musculocutaneous vessels.

Studies on the free flap by Taylor and Daniel^{21,22} were published in 1973, and a few years later the musculocutaneous flap was revived by McCraw^{23–25} and Mathes and Nahai.²⁶ Both procedures demanded a precise knowledge of the vascular supply of the tissue transfers. In the search for new donor sites for tissue transfer, surgeons returned to the dissection room. In the 1980s the pedicled musculocutaneous flap and the free microvascular transfer gained popularity and their use became common. However, on occasion there was a tendency for the techniques to neglect the aesthetic side of plastic surgery. The results could sometimes be what McDowell²⁷ described as “globs and blobs”.

To escape from the hamburger of muscle and skin, surgeons soon rediscovered that blood vessels follow fascial planes and, starting in the 1980s, there was a much greater awareness of the fasciocutaneous flap.²⁸ With this development, there has been an explosion of new terms and new classifications of the cutaneous circulation. The thesaurus of flaps now includes a bewildering array of terms including axial, random, direct cutaneous, musculocutaneous, fasciocutaneous, supercutaneous, septocutaneous, chimeric, retrograde, antegrade, and perforator. Indeed, there has been an attempt to classify flaps into no less than 10 types and subtypes on the basis of the origin of the cutaneous perforators.²⁹ In many ways, these flap classification terms are simply different expressions of the basic cutaneous architecture that Manchot published in 1889⁴ and Salmon reported in 1936.⁸ In an effort to standardize the literature and add clarity to descriptions of flaps, we have previously suggested using the name of the main source

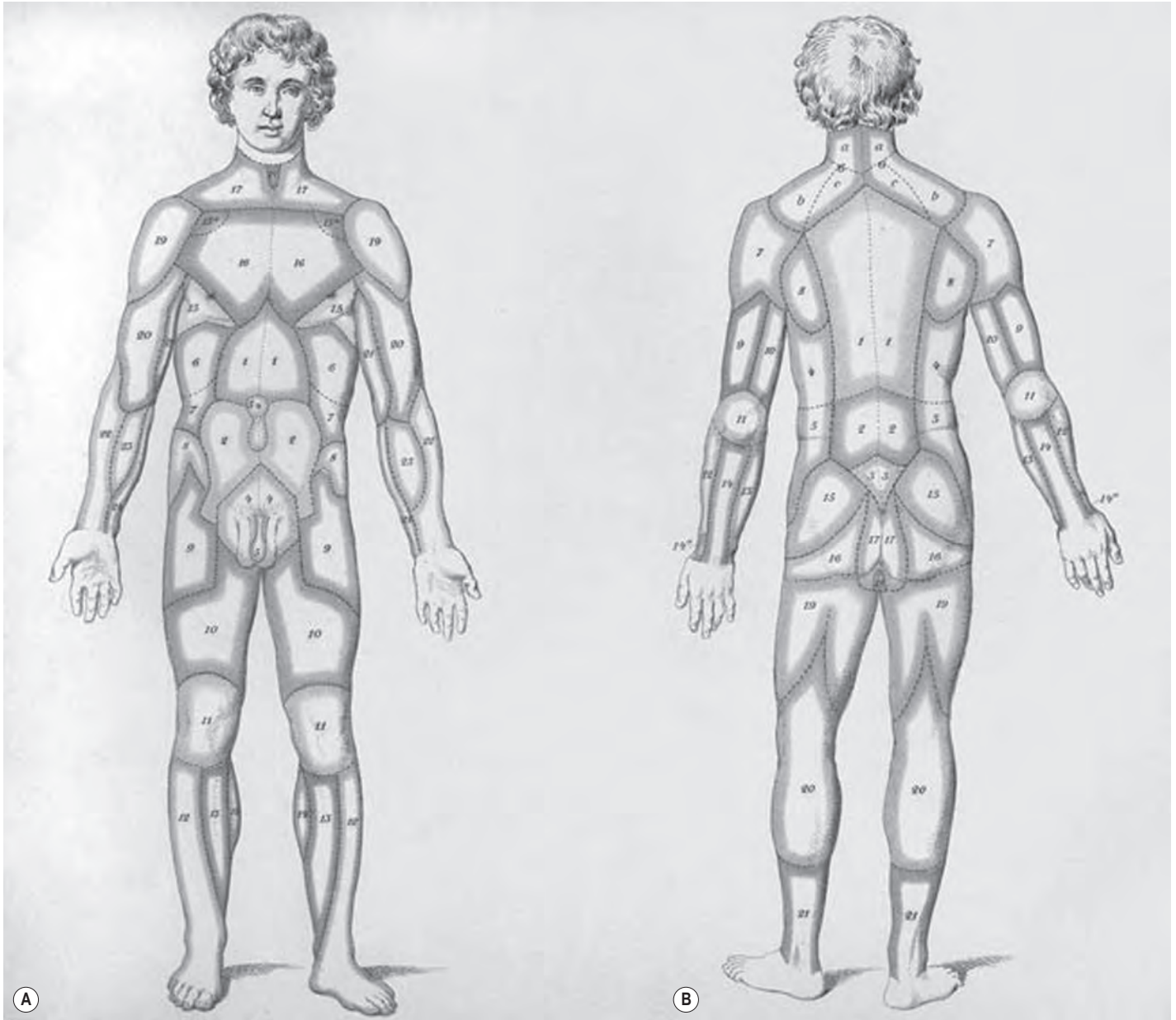


Fig. 21.3 Carl Manhot's vascular territories of the human integument. (A) Cutaneous vascular territories, ventral surface. (B) Cutaneous vascular territories, dorsal surface. (From Manhot C. *Die Hautarterien des menschlichen Körpers*. Leipzig: FCW Vogel, 1889.)

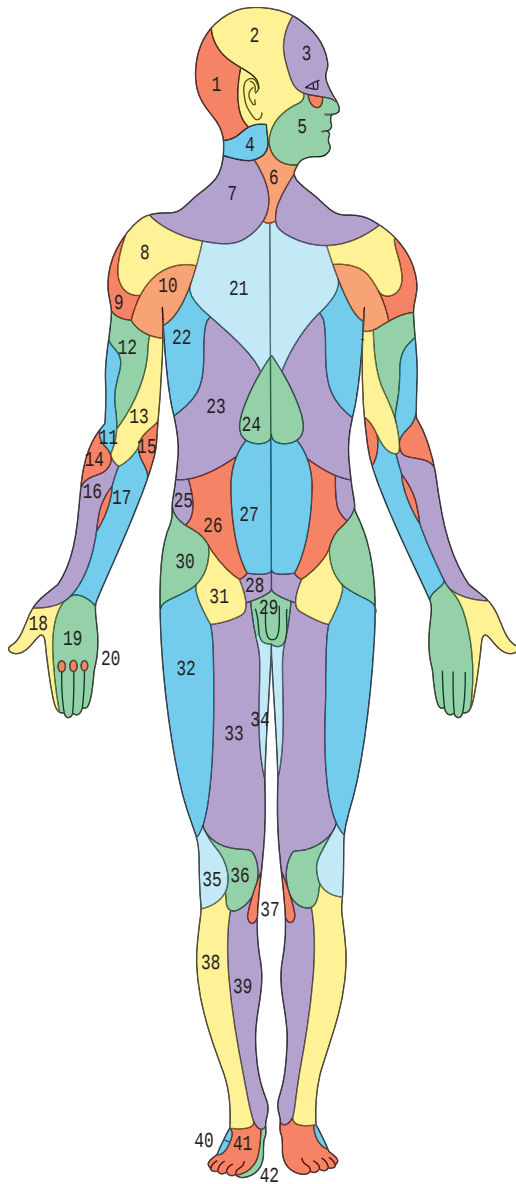


Fig. 21.4 Michel Salmon's vascular territories of the human integument, 1936. Summary of the cutaneous arterial territories of the ventral surface of the body. (From Salmon M. *Artères de la peau*. Paris: Masson, 1936.)

vessel to define the flap.^{30,31} Cormack and Lamberty³² published a book, *The Arterial Anatomy of Skin Flaps*, that contains a concise appraisal of the history, anatomy, and clinical aspects of skin flap surgery. The relationship of vessel size to vascular territory and axially of vessels in the fasciocutaneous system has also been described by Cormack and Lamberty.³³

The vertical rectus abdominis musculocutaneous flap was described by Michael Drever in 1977.³⁴ The transverse rectus abdominis muscle (TRAM) flap reported initially by Hartrampf *et al.*³⁵ demonstrated that the skin paddle survives based on the musculocutaneous perforators of the superior epigastric vessels. The pedicled and, later, the free TRAM flap became very popular for postmastectomy breast reconstruction. As the anatomy of the musculocutaneous perforators became better understood,^{36,37} surgeons harvested less of the rectus abdominis muscle in order to preserve function of the muscle. Investigators pushed the boundaries once again with the rediscovery of the perforator flap, whereby a large abdominal skin flap can be raised with preservation of the underlying rectus muscle and hence reduce the potential problems of an abdominal incisional hernia and abdominal wall weakness. This gradual change in flap design gave rise to the deep inferior epigastric artery perforator (DIEAP) flap based on perforators of the deep inferior epigastric vessels.³⁸ This evolution of autogenous reconstruction of the breast – from pedicled TRAM flap, to free TRAM flap, to muscle-sparing free TRAM flaps, to DIEAP flaps – reflects a greater awareness of the precise anatomy of the underlying musculocutaneous perforators and an attempt to reduce donor site morbidity and improve results. As knowledge of individual perforators to the skin improved, the spectrum of flap options increased dramatically.³⁹ There has been a virtual explosion in published surgical work regarding perforator flaps.

The recent enthusiasm for perforator flaps has heightened awareness of the vascular supply to tissues of the body.⁴⁰ Instead of 10–20 named arterial flaps in the body we now have a vast array of flap options based on any one of the over 400 arterial perforators of the body. This heightened awareness has led to greater understanding of the seemingly infinite possibilities for customized flap options.

flap,⁵⁹ profunda femoris artery perforator flap,⁶⁰ and the superior and inferior gluteal artery perforator flaps.⁶¹

The investigations initially involved an analysis of various regions of the body to define possible donor sites for free skin flap transfer.⁶² The studies subsequently focused on other tissues and included the anatomic basis for the transfer of bone,⁶³ nerve,⁶⁴ and certain muscles.^{21,65} Encouraged by the success of some of the resulting clinical procedures, the authors expanded the research to investigate composite units of tissue, supplied by a single vascular system. Units of skin and tendon,⁶⁶ muscle with nerve,⁶⁷ and skin, muscle, and bone^{68–70} were analyzed. It was from this work that the angiosome concept germinated. Various regions, including the anterior abdominal wall,^{21,36,65,71} the anterior thorax,^{72,73} the lower limb, and the upper limb, were studied. The results added strength to the angiosome concept of the blood supply and revealed the interconnections that exist at all levels between adjacent vascular territories, a relationship that is evident throughout the body.⁷⁴

In cadaver vascular research, various techniques can be used to identify and study the area of interest. In the past, the integument (skin and subcutaneous tissue) was removed, and the sites of emergence of the dominant cutaneous perforators (0.5 mm diameter or more) were identified on the surface of the deep fascia with lead beads. Currently, individual perforators are easily identified on CT angiography (CTA). Approximately 400 cutaneous perforators on average were identified per body.^{40,47} The three-dimensional branching pattern of main source vessels can be identified. Previous workers, including Salmon, had made topographic boundary incisions to remove areas of skin, particularly in the lines of the groins, axillae, neck, and limb joints (Fig. 21.5). These junctional regions are of great clinical importance, and for this reason the incisions were designed to retain their continuity wherever possible. In our current techniques, using CTA, the incisions utilized for dissection are not as crucial since the pathway and branches of individual vessels are clearly documented prior to dissection.

Fig. 21.5 appears online only.

In the original studies of the vascular supply of tissues of the body, the integument was radiographed, and a montage of the entire cutaneous circulation was constructed in “plan view” (Figs. 21.6, 21.7).⁴⁷ Although Manchot and Salmon described the origin and course of the cutaneous arteries, and Salmon⁹ made a separate study of the individual muscles, neither worker illustrated the course of the arteries between the deep tissues and the skin. Therefore, the skin and subcutaneous tissues were cut into parallel strips and placed on their side, and radiographs were taken to provide “elevation views” of the vessels in different regions of the body (Fig. 21.8). Current CTA techniques allow a far more detailed three-dimensional appraisal of the vascular anatomy of tissues (Fig. 21.9).

Fig. 21.6 appears online only.

All cutaneous perforators of diameter greater than 0.5 mm were traced to their underlying source arteries. The results were averaged from each cadaveric study and plotted on a diagram of the body (Fig. 21.10). Subsequently, investigations were expanded to map out the venous territories (venosomes) of the body along with the neurovascular territories of the skin and muscle.⁴⁸ These results have led to an overall picture of the vascular territories of the entire body. The remainder of

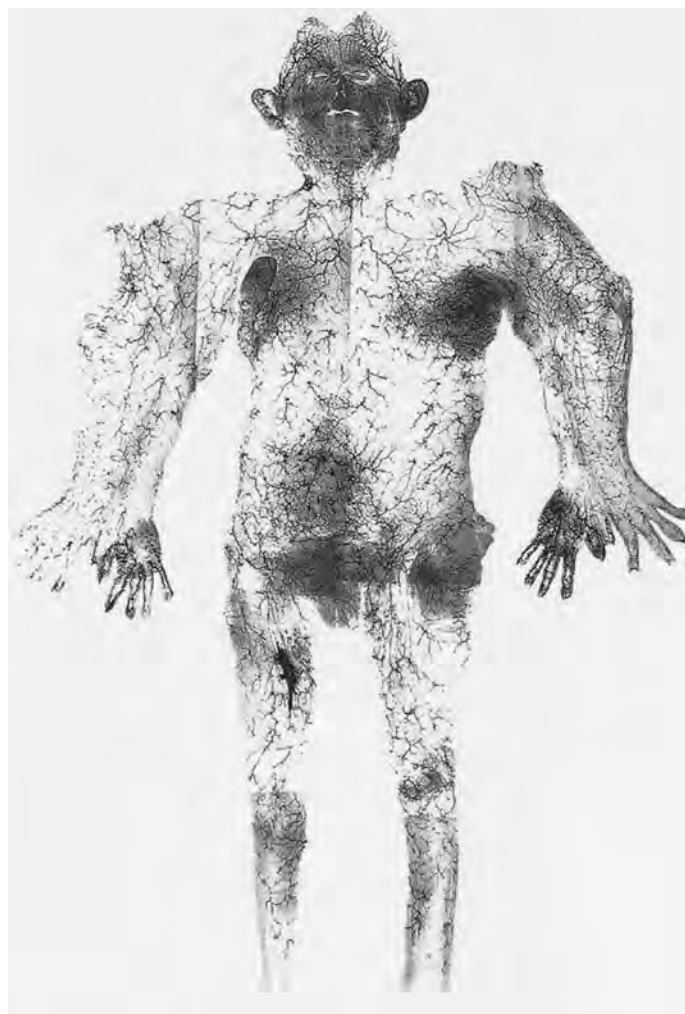


Fig. 21.7 Montage of the cutaneous arteries of the body. The skin has been incised along the ulnar border in the upper extremities, and the integument has been removed with the deep fascia on the left side and without it on the right. Note: (1) the direction, size, and density of the perforators, which are large on the torso and head and become progressively smaller and more numerous toward the periphery of the limbs; and (2) the reduced-caliber (choke) anastomotic arteries, which link the perforators into a continuous network. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

this section gives a brief overview of the arterial, venous, and nervous territories of the body.

Arterial territories

The arterial network of the body forms a continuous interlocking arcade of vessels throughout each tissue and throughout the body, linked by reduced caliber choke anastomotic vessels or true anastomoses. The course of the cutaneous perforators depends on the proximity of the source artery to the undersurface of the deep fascia. As Michel Salmon noted in 1936,⁸ arteries supply branches to each tissue that they pass, including the intermuscular septae, fascia, nerves, and tendons. Arteries generally fall into two groups, direct and indirect (Fig. 21.11). In our anatomical dissections, it is clear that there is great variability in the exact course and size of individual perforators; however, the main source vessels are relatively consistent. The direct cutaneous vessels pass

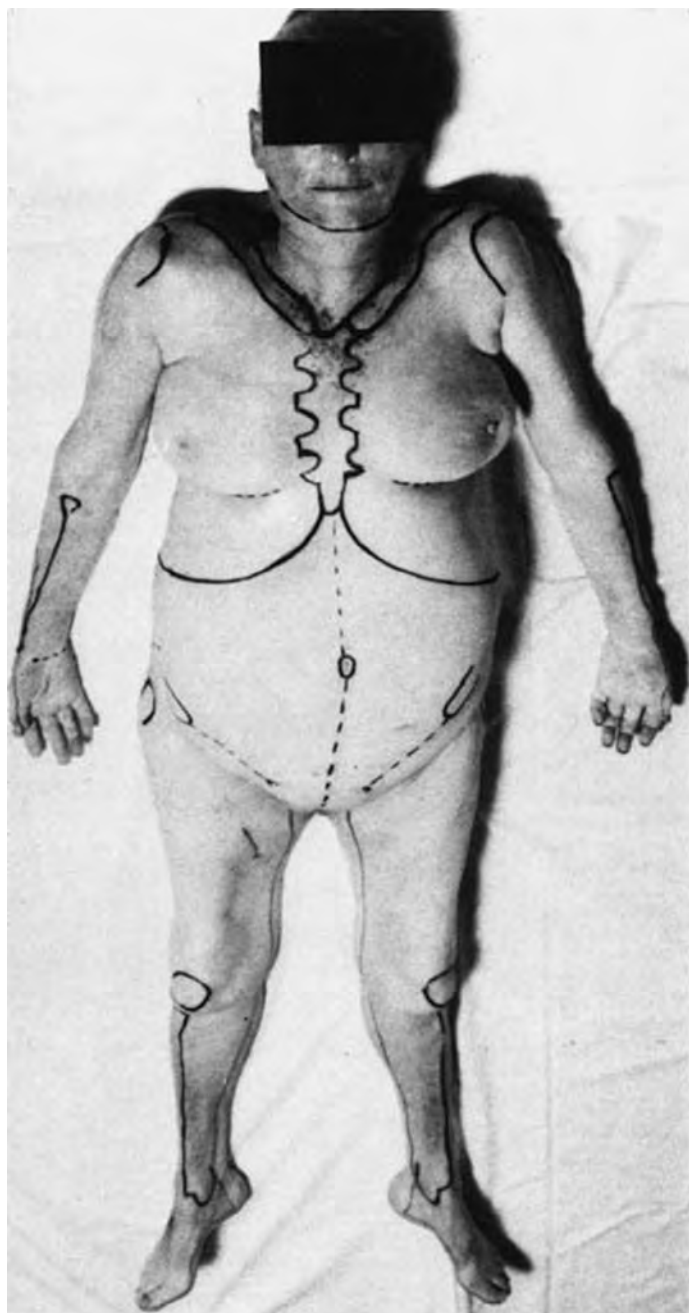


Fig. 21.5 Cadaver with body landmarks and incision lines marked. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)



Fig. 21.6 Lateral view of one female subject (A) and anterior view of another (B). (A) The arm has been removed. Note the network of large vessels that sweep laterally from the ventral and dorsal midlines, ascend from the groins, descend from the shoulder girdle, and converge on the summits of the scalp and the breasts. This demonstrates the principle that vessels radiate from fixed concave zones and radiate to mobile convex areas. (B) A lower midline scar interrupts the vessels with compensatory opening of a large choke vessel above the umbilicus (arrow) to re-establish the flow across the midline. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

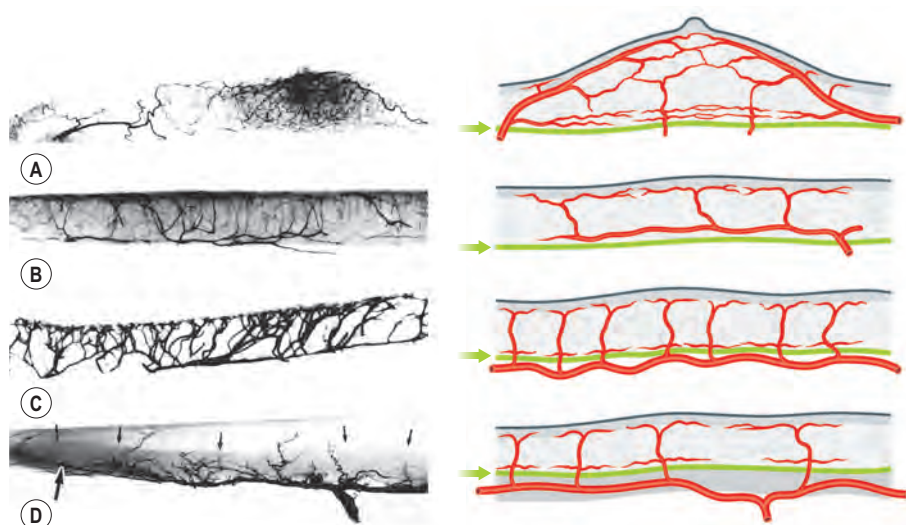


Fig. 21.8 Sectional strip radiographic studies of the breast (A), thigh (B), sole of the foot (C), and buttock (D). (D) includes the underlying gluteus maximus muscle. The schematic diagram illustrates the dominant horizontal axis of vessels that provides the primary supply to the skin in each case and its relationship to the deep fascia (arrow). (A) They predominate in the subdermal plexus. Note from left to right the internal thoracic perforator and lateral thoracic artery converging on the nipple in the radiograph of the loose skin region of the torso. (B) They are seen coursing on the surface of the deep fascia in this relatively fixed skin area. (C) The source artery itself is the dominant horizontal vessel supplying the skin, coursing beneath the deep fascia in this rigidly fixed skin region. (D) Small arrows define the deep fascia, and the large arrow indicates the large fasciocutaneous branch of the gluteal artery, which descends with the posterior cutaneous nerve of the thigh. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

between the deep tissues before piercing the outer layer of the deep fascia. They are usually the primary cutaneous vessels and their main destination is the skin. They tend to supply the skin with larger-diameter vessels which have a large vascular territory (e.g., circumflex scapular artery). The direct branches include direct cutaneous vessels (sometimes called axial vessels) and septocutaneous vessels. The indirect vessels can be considered the secondary cutaneous supply. They emerge from the deep fascia as terminal branches of arteries which supply the muscles and other deep tissues. The majority of indirect branches are musculocutaneous perforators which emerge to supply the skin. In fact, there is usually significant variability in the distribution of direct and indirect vessels and their vascular territory from individual to individual. There is a vast interconnected network of direct and indirect arteries which supply the skin. The vascular territories of individual perforators vary and tend to be reciprocal with adjacent arterial vascular territories according to the so-called

law of equilibrium, described by Salmon and supported by our work.

The direct cutaneous vessels arise from: (1) source arteries just beneath the deep fascia (e.g., the superficial inferior epigastric artery); (2) direct continuation of the source artery (e.g., the cutaneous branches of the external carotid artery); (3) deeply situated source artery or one of its branches to a muscle; they follow the intermuscular septa to the surface (e.g., septocutaneous branches of the lateral circumflex femoral artery). Indirect cutaneous vessels generally emerge from the main source artery as it courses on the undersurface

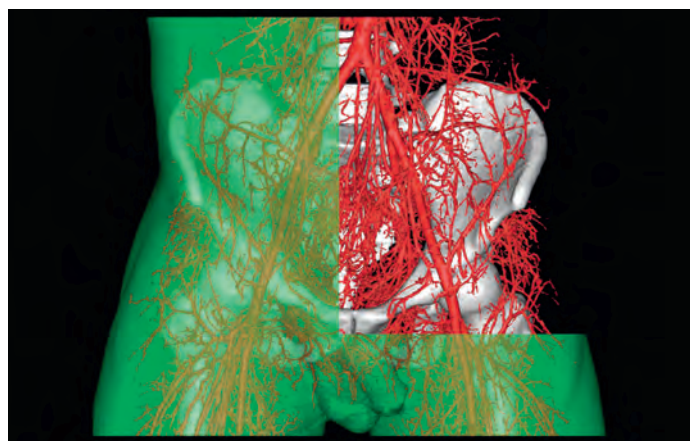


Fig. 21.9 Computed tomography angiography of a cadaver pelvis, showing bony, vascular, and skin three-dimensional anatomy. Using MIMICS software, the various anatomic structures can be included or removed. (From Morris SF, Tang M, Almutairi K, et al. *The anatomic basis of perforator flaps*. Clin Plast Surg. 2010;37:553–570.)

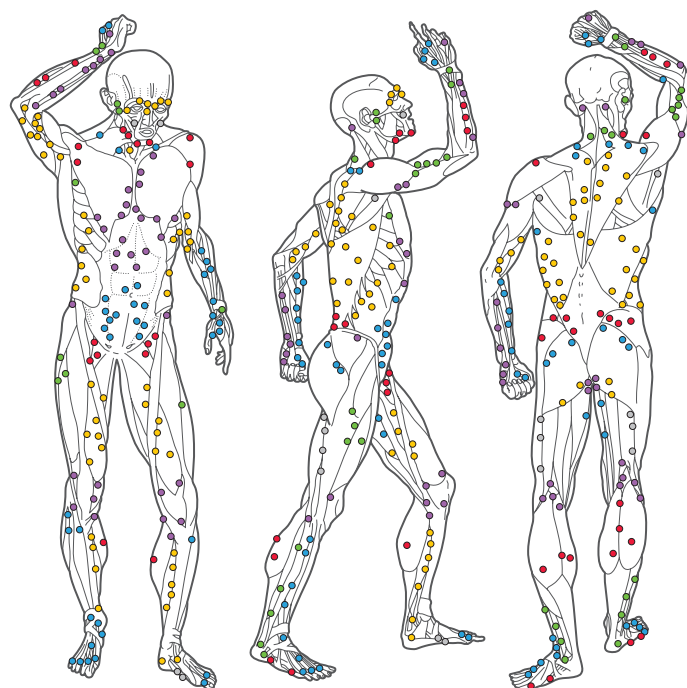


Fig. 21.10 Map of the arterial perforators of 0.5 mm diameter or more, which are color-coded to correspond to the underlying parent arteries and course with the associated perforating veins. They provide the basis for perforator flaps. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

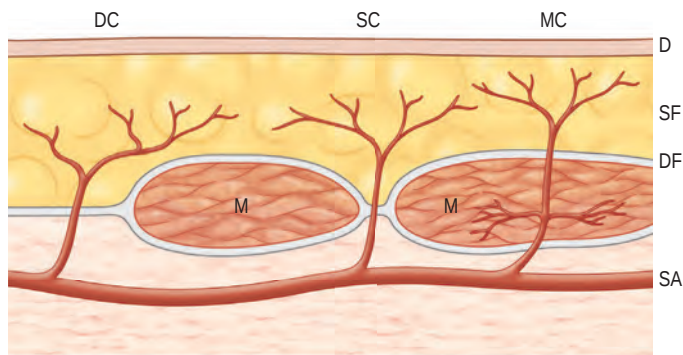


Fig. 21.11 Schematic illustration of direct and indirect cutaneous vessels. D, dermis; DC, direct cutaneous; DF, deep fascia; M, muscle; MC, musculocutaneous; SA, source artery; SC, septocutaneous; SF, superficial dermis. (From Geddes CR. *MSc Thesis. Dalhousie University, Halifax, Nova Scotia, Canada.*)

of a muscle and penetrate through the muscle; e.g., musculocutaneous perforators of the deep inferior epigastric arteries (DIEA). In the human body, there are approximately 400 perforators, about 40% of vessels are direct and 60% indirect perforators.

The direct cutaneous perforators pierce the deep fascia near where it is anchored to bone or the intermuscular and intramuscular septa (see Fig. 21.10). These lines and zones of fixation also correspond to the fixed skin areas of the body. From these points, the vessels flow toward the convexities of the body surface, branching within the integument. In general, the wider the distance between the cavities and the higher the summit, the longer the vessel (see Fig. 21.8). The size and density of the direct perforators also vary in different regions. For example, in the head, neck, torso, arm, and thigh, the vessels are larger, longer, and less numerous. In the forearm, leg, and dorsum of the hands and feet, the vessels tend to be smaller, shorter, and more numerous. In the palms of the hands and the soles of the feet, where the skin is fixed, there is a high density of smaller perforators. Hence, the primary supply of each cutaneous territory varies between source arteries. Each of these territories also has indirect perforators.

The course of the cutaneous perforators between the deep fascia and the skin also varies in different regions. Regardless of their site, however, they follow the connective tissue framework of the superficial fascia, interconnecting at all levels. They ramify on the undersurface of the subcutaneous fat adjacent to the deep fascia and then branch and course toward the subdermal plexus, working their way between the fat lobules. The smaller vessels tend to course vertically toward the skin, whereas the larger vessels branch in all directions in a stellate pattern or course in a particular axis, branching as they pass parallel to the skin surface.

In the scalp and limbs, where the skin is relatively fixed to the deep fascia, the larger vessels hug that surface. They course on the deep fascia for a considerable distance in the loose areolar layer that separates them from the subcutaneous fat (see Fig. 21.8). This is especially true when a perforator accompanies a cutaneous nerve.

In the loose skin areas of the body, the direct cutaneous vessels course for a variable distance parallel to the deep fascia. They are more intimately related to the undersurface of the subcutaneous fat, however, being plastered to it by a thin fascial sheet that separates them on their deep surface

from a plexus of smaller vessels. This plexus lies in loose areolar tissue on the surface of the deep fascia. It is formed by branches that arise from the direct perforators as they pierce the deep fascia and the connections these branches make with smaller indirect perforators. The large direct perforators then pierce the subcutaneous layer. They ascend within the superficial fascia (subcutaneous fat) to reach the rich subdermal plexus, where they travel for considerable distances (see Fig. 21.8).

Within the deep tissue, whether muscle, tendon, nerve, or bone, a pattern similar to that in the integument exists, with a three-dimensional network of vessels interlinking between vascular territories, the perimeters of which are linked by choke arteries. Within the muscles, these choke vessels often exhibit a characteristic corkscrew appearance on angiography.

Venous drainage

The cutaneous veins also form a three-dimensional plexus of interconnecting channels throughout the body (Fig. 21.12). There are valved segments in which valves direct flow in a particular direction, and there are avalvular segments where no valves are present. The avalvular or oscillating veins allow bidirectional flow between adjacent venous territories. They connect veins whose valves may be oriented in opposite directions, thus providing for the equilibration of flow and pressure. Indeed, there are many veins whose valves direct flow initially in a distal direction, away from the heart, before joining veins whose flow is proximal. An example of this is the superficial inferior epigastric vein that drains the lower abdominal wall integument toward the groin. In some regions, valved channels direct flow radially away from a plexus of avalvular veins, for example, in the venous drainage of the nipple–areola complex. In other areas, valved channels direct flow toward a central focus, as seen in the stellate branches of the cutaneous perforating veins of the limbs.

In general, venous anatomy parallels arterial anatomy (Fig. 21.13). From dermal and subdermal venous plexuses, the veins collect either into horizontal large-caliber veins, where they often relate to cutaneous nerves and a longitudinal system of chain-linked arteries, or alternatively in centrifugal or stellate fashion into a common channel that passes vertically down in company with the cutaneous arteries to pierce the deep fascia. Thereafter, the veins travel with the direct and indirect cutaneous arteries, draining ultimately into the venae comitantes of the source arteries in the deep tissue.

In general, the origin, course, and distribution of the deep veins (vena comitantes) are a mirror image of the deep source arteries, but they are larger and more plentiful. Although the anatomy of the veins is subject to considerable variation between sides in the same individual as well as between other individuals, the pattern of venous arcades is evident throughout. These arcades generally become smaller and more numerous as the periphery of the region or the tissue is reached. The superficial veins, however, are independent of the deep arteries (e.g., greater saphenous vein, cephalic vein) and may have a different area of drainage. For example, in the forearm there are paired vena comitantes to the radial and ulnar arteries but a separate system of large-caliber subcutaneous veins, including cephalic, basilic, and antebraclial veins.

The site and density of the valves within the deep venous network are variable. The deep veins follow the bony skeleton



Fig. 21.12 The venous network of the integument of a female subject. This is a montage of venograms from an injection study. (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories [venosomes] of the human body: experimental study and clinical implications*. *Plast Reconstr Surg*. 1990;86:185.)

of the body or the intermuscular septa with their associated arteries. In some regions, these veins are single; in others, they are duplicated as *venae comitantes*. In the limbs, the veins commence distally in the hands and feet as single channels linked by venous arcades. These arcades become progressively larger as they approach the wrist and ankle. The veins are duplicated in the forearm and leg, and each pair of veins

is linked by a rich stepladder of venous channels that are usually free of valves. These *venae comitantes* then reunite to form single channels. In the lower limb, this occurs in the popliteal fossa, but in the upper limb, the union is most commonly in the proximal arm or even as high as the axilla.

In the torso, the pattern of arcades is conspicuous (see Fig. 21.13); the parent veins are oriented as longitudinal and transverse arcades that match the pattern of the source artery. Distinct territories are evident. Where choke arteries define the arterial territories, they are matched by oscillating veins in the venous network. The existence of *venae comitantes* is variable.

Within the muscle, the intramuscular venous network mirrors that of the arterial side. Where arterial territories are linked by choke arteries or true anastomotic arteries without changing caliber, the venous territories of the muscles, which drain in opposite directions, are linked by avalvular oscillating veins. Broadly, the muscles can be classified into three types on the basis of their venous architecture. Type I muscles have a single venous territory that drains in one direction. Type II muscles have two territories that drain from the oscillating vein in opposite directions. Type III muscles consist of three or more venous territories that drain in multiple directions (Fig. 21.14).

The extramuscular veins are of two types. The first group consists of the efferent veins. They contain valves and drain the muscles to their parent veins. The other group consists of the afferent veins. They are derived from the overlying integument as musculocutaneous perforators or from adjacent muscles (see Fig. 21.14).

Neurovascular territories

In our anatomical studies of neurovascular territories, fresh human cadavers were injected with a radiopaque lead oxide mixture, and the nerves were dissected and labeled with fine computer wire.⁴⁹ The nerves and vessels were then segregated by subtraction angiography.

The most obvious feature seen throughout the skin and muscle is the linear arrangement of the nerves and their branches, compared with the looping arcades of the interconnecting vessel network, with the nerves taking the shortest route between two points. In general, the orientation of cutaneous nerves is longitudinal in the limbs, transverse or oblique in the torso, and radiating from loci in the head and neck. Of particular note is that the cutaneous nerves, like the arteries, pierce the deep fascia at fixed skin sites.

Each cutaneous nerve is accompanied by an artery, but the relationship is variable. Some of the arrangements seen in the integument are shown in Fig. 21.15. In each case, either a long artery or a chain-linked system of arteries “hitchhikes” with the nerve.

When the cutaneous nerve and artery appear at the deep fascia together, their relationship is often established early (e.g., the lateral intercostal neurovascular perforators on the torso or the saphenous system in the lower limb). However, the nerve sometimes pierces the deep fascia at a point remote from the emergence of its associated artery (e.g., the lateral cutaneous nerve of the thigh and the superficial circumflex iliac artery below the inguinal ligament; Fig. 21.16). Alternatively, the nerve leaves one vascular system with which it is traveling in parallel to cross the path of another

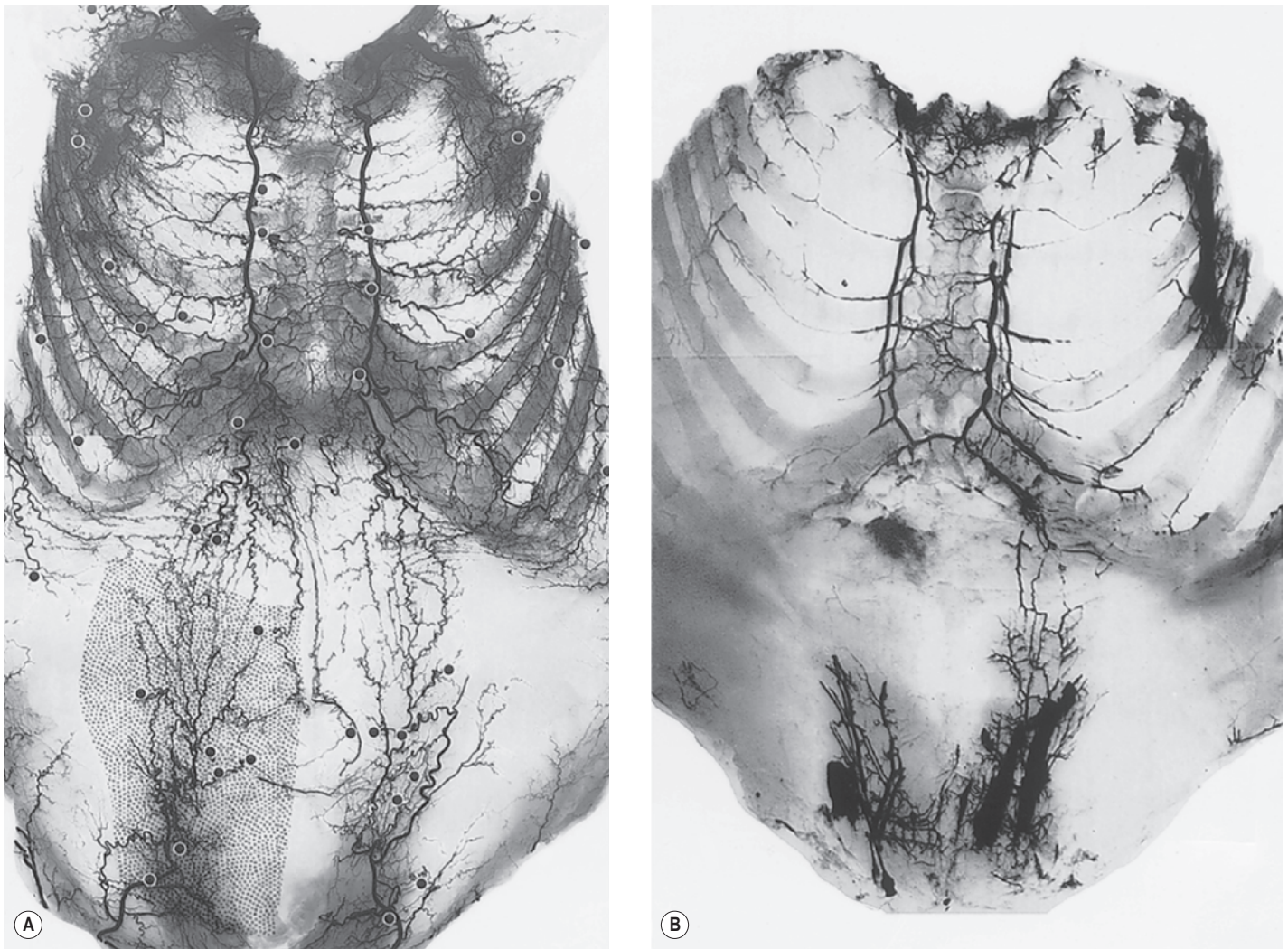


Fig. 21.13 (A) Arterial and (B) venous studies of the anterior torso. Note the “corkscrew” choke arteries that link adjacent territories in the arterial study and the mixture that has extruded from the deep inferior epigastric veins as a result of the resistance of the valves. Radiographic lead beads identify the origin of the cutaneous perforators from their source vessels in the arterial study. (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories [venosomes] of the human body: experimental study and clinical implications*. Plast Reconstr Surg. 1990;86:185.)

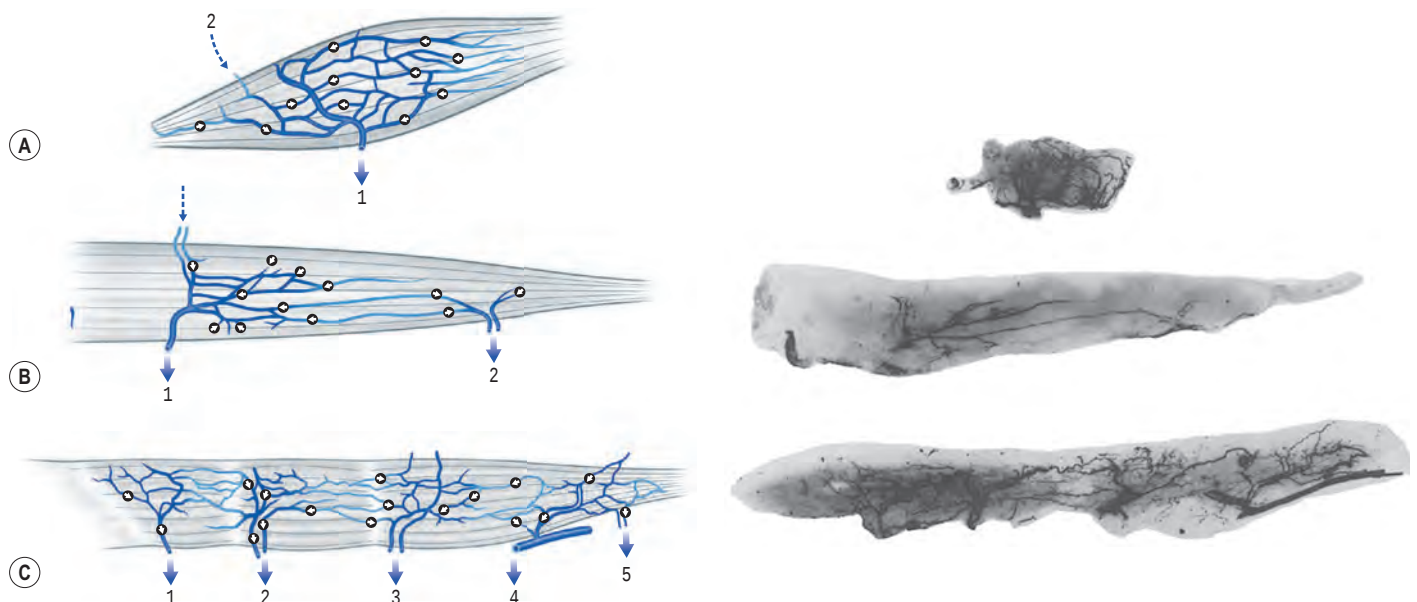


Fig. 21.14 Illustrations and radiographs of venous injection studies of the supraspinatus (A), gracilis (B), and sartorius (C) muscles. Note the oscillating veins that separate them into type I, II, and III muscles and the efferent veins entering the supraspinatus and gracilis muscles (dashed arrows). (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories [venosomes] of the human body: experimental study and clinical implications*. Plast Reconstr Surg. 1990;86:185.)

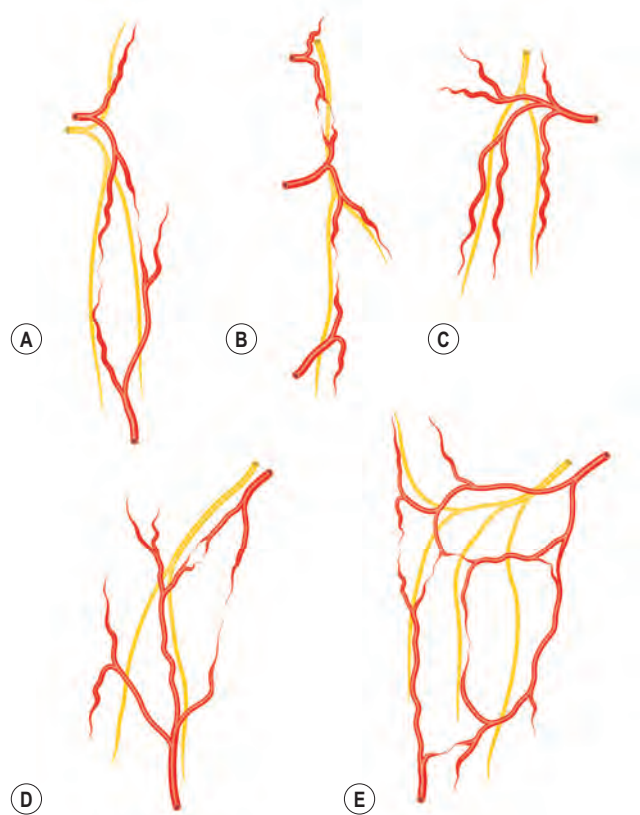


Fig. 21.15 The neurovascular patterns found in the integument. **(A)** A long artery connected to its neighbor by a true anastomosis courses with the nerve. **(B)** A chain-linked system of arteries hitchhikes with the nerve. **(C)** The nerve and artery pierce the deep fascia at separate sites. Branches of the vessel peel off to accompany the nerve as it crosses the main arterial trunk. **(D)** The nerve at first courses parallel to an artery and then approaches the neighboring artery from its periphery to descend along its branches toward the main trunk. **(E)** The nerve crosses the primary and secondary arcades of the artery before coursing parallel to the vascular network. (From Taylor GI, Gianoutsos MP, Morris SF. *The neurovascular territories of the skin and muscles: anatomic study and clinical implications*. Plast Reconstr Surg. 1994;94:1.)

(e.g., the lateral intercostal nerve, which courses initially with its artery and then leaves it to meet the superficial inferior epigastric vessel). In many of these cases, secondary or tertiary branches of the artery often peel off to accompany the nerve (see Fig. 21.16). Sunderland noted that each peripheral nerve is abundantly vascularized by a “vascular net” of a series of nutrient arteries entering the nerve at different levels.⁷⁵

Fig. 21.16 appears online only.

The vascular architecture of the intramuscular veins and arteries is almost identical for each muscle. Therefore, to simplify the description of the nervous supply to the muscles, only the arterial relations of the nerves are discussed and illustrated. The intramuscular branches of the nerves were dissected to, but not within, the individual muscle bundles. The following observations were made:

1. The nerves follow the connective tissue framework. Dissection showed the motor nerves coursing in the connective tissue sheath from its origin at the nerve trunk to the neurovascular hilum of the muscle. Thereafter, the nerve and its branches follow the

intramuscular connective tissue to reach the muscle bundles.

2. The nerves are economical. As in the integument, the direct course of the motor nerves is in stark contrast to the wandering pattern of the vessels. The nerves take the shortest extramuscular and intramuscular routes compatible with the function of each muscle.
3. Neurovascular relations vary with the muscle, the extramuscular course, and the intramuscular branching of the nerves and the vessels. Some muscles have a single nerve supply; others receive multiple motor branches. All receive multiple arterial pedicles. However, despite the variables, certain observations can be made:

- Each motor nerve is accompanied by a vascular pedicle, but the reverse does not apply.
- The motor nerve is usually accompanied by the dominant vascular pedicle. There are exceptions to this, however. For example, the nerve supply to sternocleidomastoid is usually accompanied by a minor vascular pedicle.
- The nerve may enter the muscle before branching.
- Once within the muscle, the nerve divides early, and its branches sweep rapidly into position, parallel to the muscle fibers. The vessels, however, branch and form primary and secondary arcades, often crossing the muscle bundles and nerves before tertiary and quaternary branches are provided to the muscle fibers.

Ultimately, the terminal branches of the vessels and nerves come into close contact and course together in the connective tissue framework parallel to the muscle bundles.

Neurovascular anatomy of muscles of the body

Several methods have been used to classify muscles on the basis of morphology, function, blood supply, or nerve supply (Table 21.1). We have classified muscles of the body according to their most common pattern of innervation (Fig. 21.17). The pattern of neurovascular anatomy of the muscles influences the way a whole muscle or segment of muscle can be harvested as a functioning muscle microvascular transfer. It is possible to subdivide certain muscles, based on the neurovascular anatomy, into separate neurovascular units if each segment has an individual vascular pedicle. Clinically, serratus anterior, latissimus dorsi, gracilis, and rectus femoris are often used in this way, taking a portion of the muscle with their motor nerve and blood supply.^{55,56}

- Type I. The muscle is supplied by a single motor nerve that divides after entering the muscle (Fig. 21.18). Multiple vascular pedicles supply each muscle and form a continuous network throughout the tissue. It is possible in each case to remove a vascularized segment of muscle with its nerve supply and yet leave viable muscle *in situ*.
- Type II. A single motor nerve supplies each of the muscles in this group, but the nerve divides before entering the muscle. Muscles in this group include the deltoid (see Fig. 21.18), gluteus maximus, trapezius, vastus lateralis, serratus anterior, and flexor carpi ulnaris.



Fig. 21.16 Arterial injection of the right upper limb and torso. **(A)** Note the chain-linked systems of arteries (arrows) that course with the cutaneous nerves in the upper limb. **(B)** On the torso, the nerves are marked on the arterial study. They course with the cutaneous arteries, cross them at angles and collect arterial branches, or approach the arteries from opposite directions (arrows). (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113; and Taylor GI, Gianoutsos MP, Morris SF. *The neurovascular territories of the skin and muscles: anatomic study and clinical implications*. Plast Reconstr Surg. 1994;94:1.)

Table 21.1 Classification of muscles based on their nerve supply

Type I	Type II	Type III	Type IV
Latissimus dorsi	Deltoid	Gastrocnemius	Rectus abdominis
Extensor indicis	Gluteus maximus	Sartorius	Levator scapulae
Extensor pollicis longus	Trapezius	Tibialis anterior	Internal oblique
Abductor pollicis longus	Vastus lateralis	Flexor digitorum superficialis	Digastric
Palmaris longus	Serratus anterior	Subscapularis	Erector spinae
Teres minor	Flexor carpi ulnaris	Teres major	
Extensor hallucis longus	Biceps brachii	Triceps	
Plantaris	Brachialis	Extensor carpi ulnaris	
Popliteus	Flexor pollicis longus	Extensor digitorum longus	
	Flexor hallucis longus	Gluteus medius	
	Pectineus	Gluteus minimus	
	Adductor longus	Vastus medialis	
	Adductor brevis	Vastus intermedius	
		Peroneus longus	
		Soleus	
		Tibialis posterior	

- Type III. Multiple motor nerve branches derive from the same nerve trunk (see Fig. 21.18). Once again, it is possible to subdivide each muscle into separate functional units because of the multiple vascular pedicles as well as the several nerve branches. Gastrocnemius is often split in this way, taking one head for reconstruction, leaving behind the other functional unit with its neurovascular supply attached.
- Type IV. Multiple motor nerves are derived from different nerve trunks (see Fig. 21.18). It is apparent that each muscle can be subdivided anatomically into several functional units because of the multiple, often segmental neurovascular pedicles. Indeed, several of these muscles are formed developmentally by the fusion of adjacent somites (e.g., rectus abdominis and internal oblique).



Access the Comparative Anatomy section, including Figs. 21.19–21.21, online at

<http://www.expertconsult.com>

The angiosome concept

Following a review of the works by Manchot and Salmon, along with the results of our total body studies of blood supply to the skin and the underlying deep tissues, it has been possible to divide the body anatomically into three-dimensional vascular territories named angiosomes. Each of these three-dimensional angiosomes is supplied by a source (segmental or distributing) artery and its accompanying vein or veins (Figs. 21.22–21.24). Each angiosome can be subdivided into

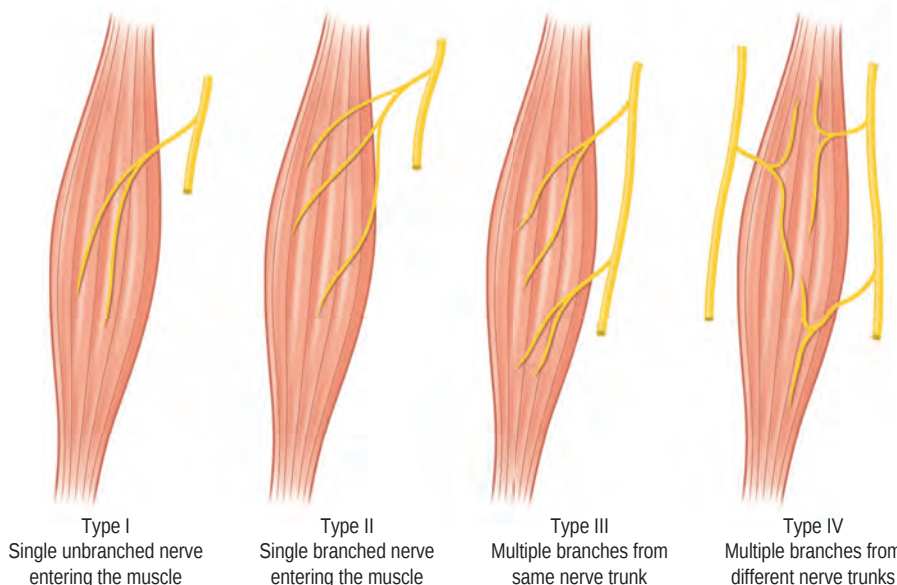


Fig. 21.17 Classification of muscle on the basis of nerve supply. (From Taylor GI, Gianoutsos MP, Morris SF. *The neurovascular territories of the skin and muscles: anatomic study and clinical implications*. Plast Reconstr Surg. 1994;94:1.)

Comparative anatomy

In the course of parallel investigations to describe animal models for vascular studies, it was noted that there are close similarities in vascular anatomy between animal species. However, there are also important differences of which investigators should be aware. The purpose of this section is to provide a more complete picture of the vascular territories. As we shall see, the angiosome concept can be applied equally to other members of the animal kingdom as well as to humans.⁵³

In plastic surgical research, selection of various animals for the study of flap physiology is based on cost, convenience, availability, and/or ethical considerations rather than on a profound knowledge of their vasculature. The pig, for example, is a fixed-skin animal, and because human integument is also fixed in many areas, it has been assumed that this animal is therefore most ideally suited for experiments on skin flaps. It is important to understand the vascular basis of the experimental animal model since results may not be generalizable to humans.

Study of these animals also leads us to gain further insight into the development and arrangement of the vascular system. It may aid in identification of the ideal animal for other experiments, such as investigation of the delay phenomenon, use of tissue expansion, programming of vessels, and prefabrication of flaps – whether they are skin, other tissues, or combinations of tissues.

When the radiographs of four animals are reviewed (Fig. 21.19), it is obvious there is a marked dissimilarity in the vasculature of the integument between them and that of the

human (see Fig. 21.7). Surprisingly, however, this is in marked contrast to the dramatic similarity of the radiographs of deep tissue of the mammalian torsos (Fig. 21.20).

The pattern of the cutaneous vasculature of the integument ranges from the fixed skin of the pig (supplied by a large number of small vessels over most of the hemitorso) to the mobile skin of the rabbit, in which four large vessels supply the majority of this area. The duck, not surprisingly, shows considerable diversity in the vasculature of its integument. Nevertheless, basic patterns are evident, having been modified by the growth and functional demands of the species.

The similarity in vasculature of the deep tissue is not confined to the anterior torso. Certain muscles between species have a remarkably similar vascularity, as can be seen in Fig. 21.21.

It appears that the vascular blueprint of the deep tissues of the torso of mammals remains relatively constant. It is simply enlarged from the fetus to the adult and from small to large mammals. The reason for this may be that the functional requirements of the torso are the same in each mammal, that is, respiration, protection of the viscera, and aid in removal of the contents. Beyond the deep tissues of the torso, it appears that the vasculature of the overlying integument, the head and the neck, and the limbs has been modified to meet the functional demands of each species, as Hunter⁷⁶ predicted more than 200 years ago.

Similarities are also seen in comparing the torso studies of mammals with those of other species, for example, the bird. In each case, vascular arcades arise from three basic sites: cranially from the subclavian and axillary vessels (aortic arch), laterally

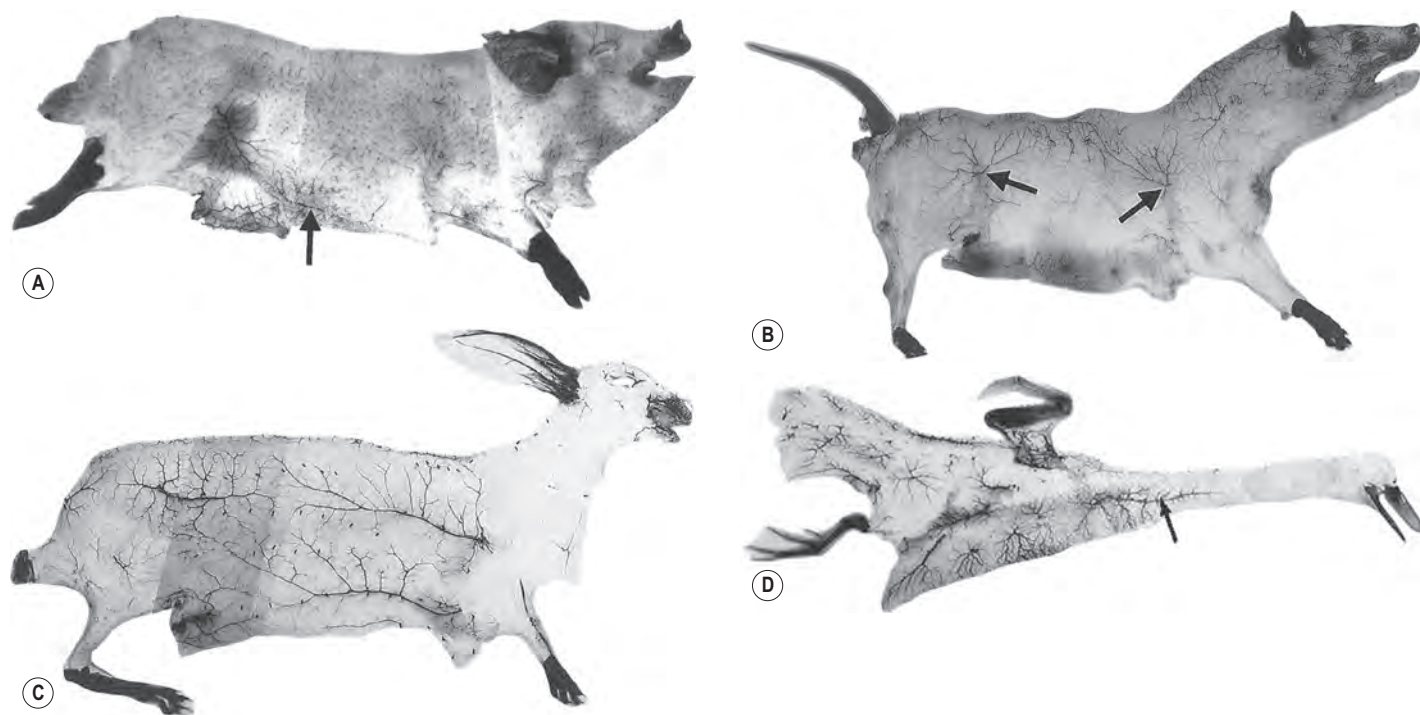


Fig. 21.19 (A) Arteriogram of the skin of the pig. Note numerous small perforators on lateral torso, a superficial vein that has filled in the study (arrow), the larger segmental vessels near the ventral and dorsal midline, and the large perforator of the deep circumflex iliac artery near the hip. (B) Angiogram of the dog. Note the large perforator of the deep circumflex iliac artery and the thoracodorsal artery (arrows) near the hip and shoulder, respectively. (C) Arteriogram of the rabbit. Note the very large perforators of the deep circumflex iliac artery and thoracodorsal arteries dorsally and the superficial inferior epigastric artery and lateral thoracic arteries ventrally. Note also the large vessels supplying the ear. (D) Arteriogram of the duck. Note the discrete territories bounded by choke arteries and the long, stretched-out perforator of the transverse cervical artery in the mobile skin area of the neck (arrow). (From Taylor GI, Minabe T. *The angiosomes of the mammals and other vertebrates*. Plast Reconstr Surg. 1992;89:181.)

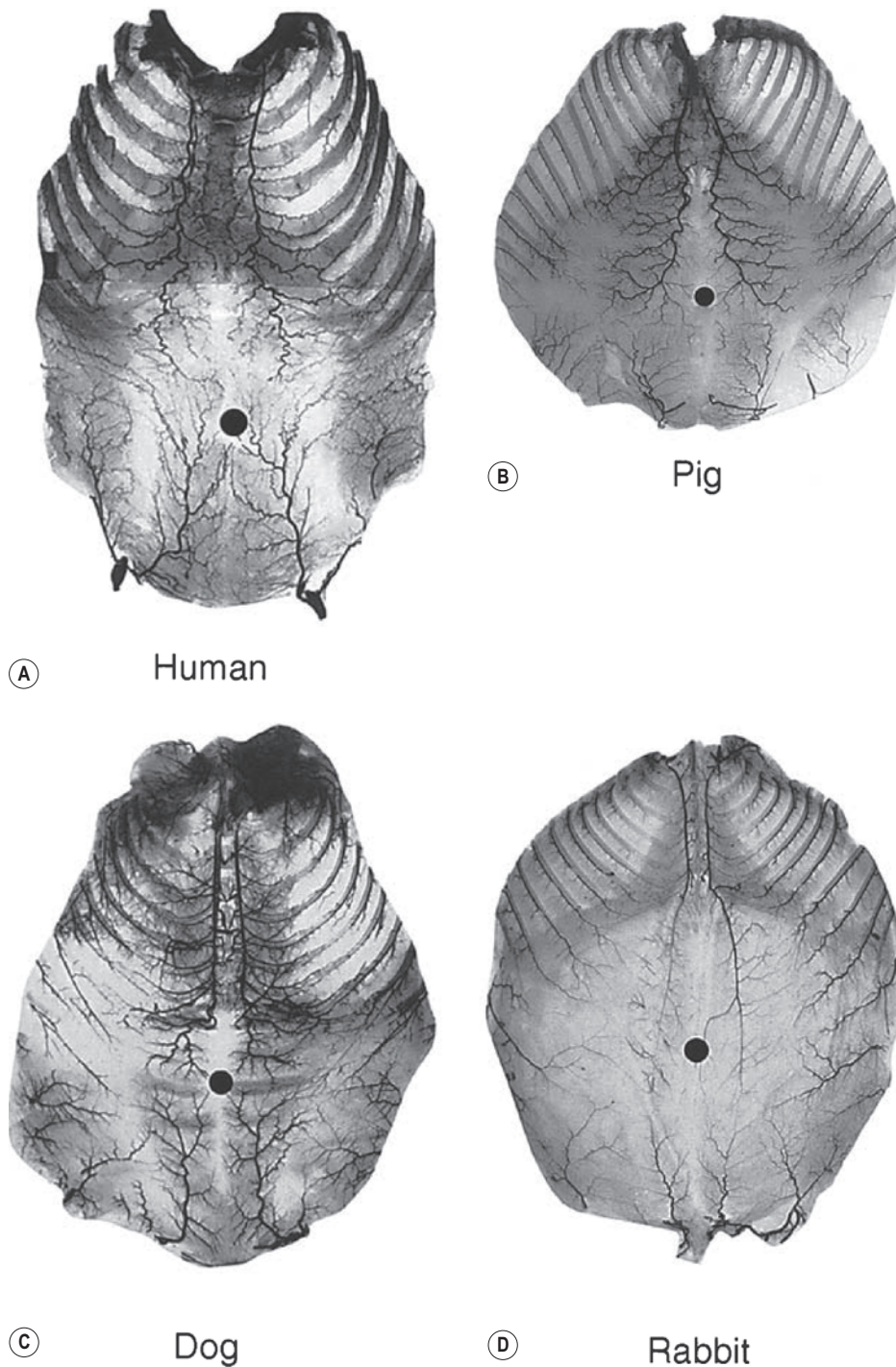


Fig. 21.20 Injection studies of the anterior torso with the integument removed and umbilicus located (large dot). The studies of the human and dog (A and C) are almost identical, with the deep inferior epigastric artery larger than the deep superior epigastric artery. In the pig and rabbit (B and D), the reverse applies. (From Taylor GI, Minabe T. *The angiosomes of the mammals and other vertebrates*. Plast Reconstr Surg. 1992;89:181.)

from the aorta (descending part), and caudally from the iliac and femoral vessels (terminal aorta). These three arcades form the basic vascular loops in the body that are common throughout the animal kingdom, including the human.

An underlying theme of the vascular architecture is that of vascular loops and arcades. Comparison of the vascular

architecture in the human with that of other animals and other species reveals a similar arrangement. In loose-skinned animals, the arcades in the integument are stretched over long distances (see Fig. 21.18). In the wings of insects and in the leaves of plants, the “veins” assume a pattern of interconnecting arcades similar to those of the intestinal mesentery.

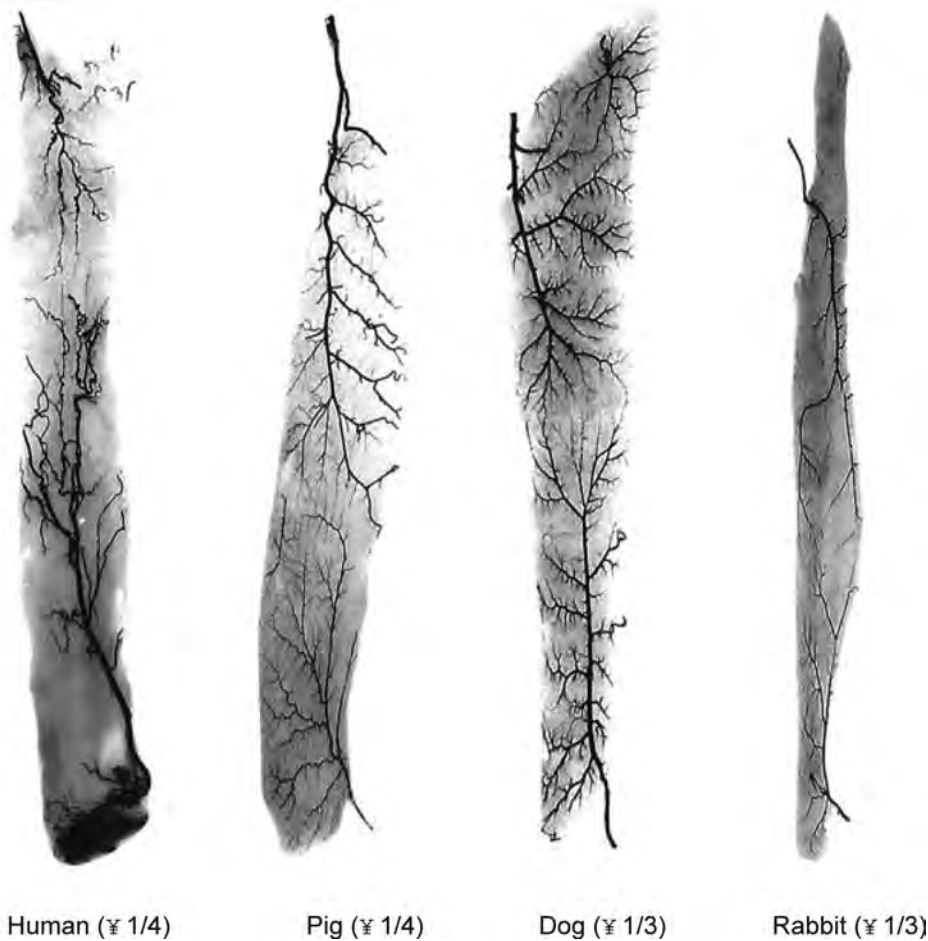


Fig. 21.21 Comparative study of the rectus abdominis muscle from the various mammals studied. There is a striking similarity between the studies. However, in all animals except the pig, the muscle extends on to the thorax more cranially than in the human, and this region of the rectus receives additional branches from the internal thoracic artery. The reciprocal size relationship of the deep superior epigastric artery and deep inferior epigastric artery between species is a good example of the law of equilibrium. (From Taylor GI, Minabe T. *The angiosomes of the mammals and other vertebrates*. Plast Reconstr Surg. 1992;89:181.)

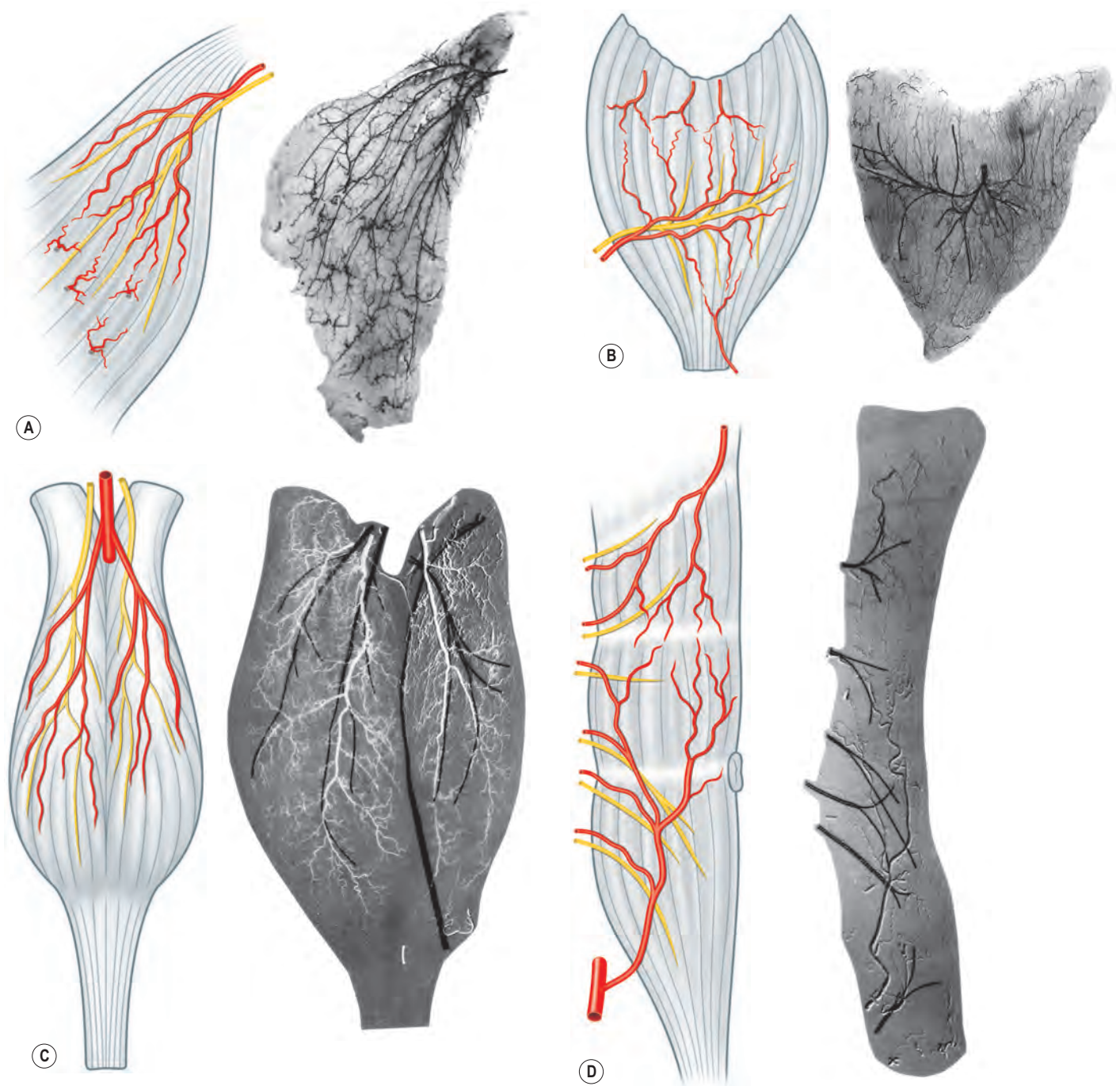


Fig. 21.18 Schematic diagram (left) of (A) type I (latissimus dorsi), (B) type II (deltoid), (C) type III (gastrocnemius), and (D) type IV (rectus abdominis) muscles to match radiograph (right) of each muscle. Nerves and vessels are seen together in the radiographs. The nerves are straight, whereas the vessels are spiral. The nerves, labeled with computer wire, appear black and the vessels pale and "ghost-like" in this subtraction study. (From Taylor GI, Gianoutsos MP, Morris SF. *The neurovascular territories of the skin and muscles: anatomic study and clinical implications*. Plast Reconstr Surg. 1994;94:1.)

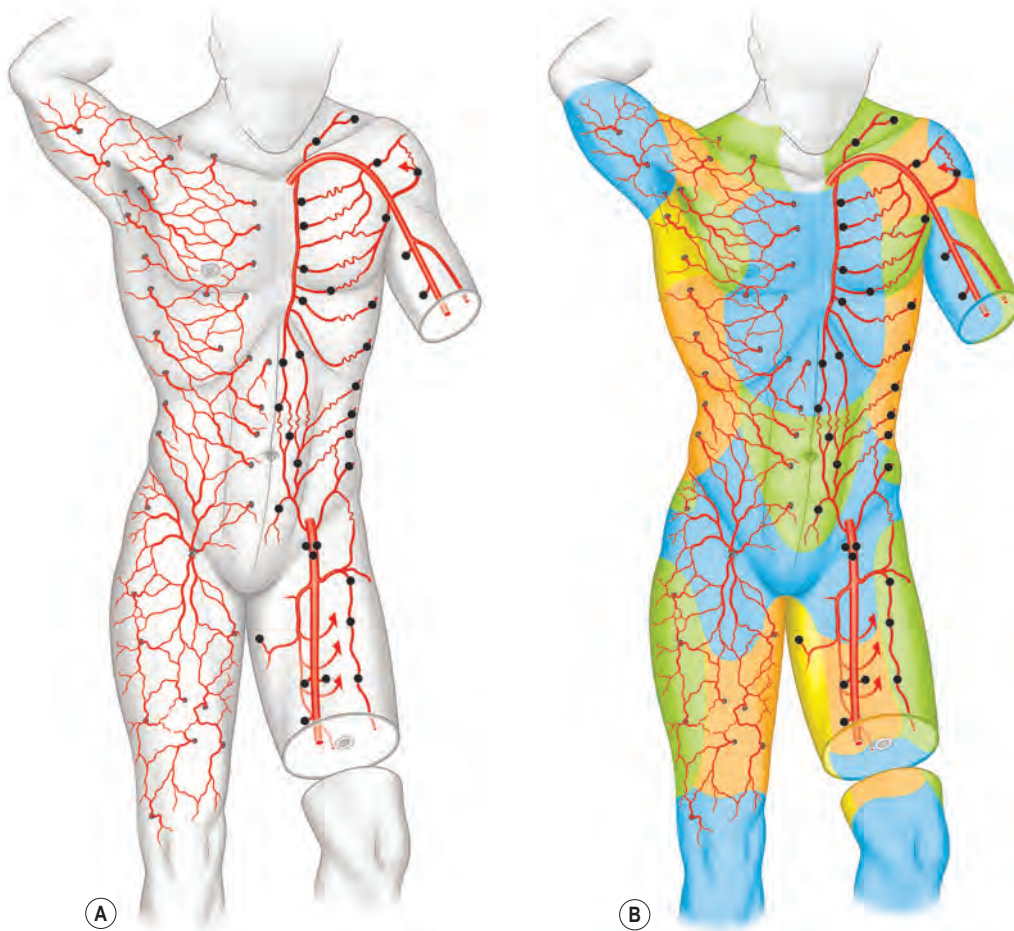


Fig. 21.22 The technique by which the angiosomes were defined. **(A)** The cutaneous perforators with their choke connections are depicted on the left. The origin of the perforators from their underlying source arteries and their muscle branches is shown on the right. **(B)** The vascular territories of each source artery are illustrated in the integument (left) and deep tissues (right) by lines drawn through the choke connecting vessels. Note that the territories correspond in these two layers and how they appear as sectors in the limbs. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

matching arteriosomes (arterial territories) and venosomes (venous territories) or into further subunits based on individual perforators to the skin. Forty of these territories were initially described,⁷³ but subsequent investigation has led to many of these territories being subdivided further into smaller composite units and revealed some that do not reach the skin surface. In a later study, 61 vascular territories were identified.⁴⁰ Recent work has illustrated no fewer than 13 angiosomes of the head and neck, originally mapped as eight supplied by branches of the external carotid, internal carotid, and subclavian arteries.⁵² The angiosome concept indicates that the three-dimensional block of tissue is supplied by a major source artery and its accompanying vein(s), but it is important to note that the angiosome itself may be divisible depending on the branching pattern of the source vessel.

These composite blocks of skin, bone, muscle, and other soft tissues fit together like the pieces of a jigsaw puzzle, to make up the vascular supply of the body. In some of the angiosomes, there is a large overlying cutaneous area and a relatively small deep tissue region; in others, the reverse pattern exists. Each angiosome is linked to its neighbor at every tissue level, either by a true (simple) anastomotic arterial connection without change in caliber of the vessel or by a reduced-caliber choke anastomosis. A similar pattern with avalvular (bidirectional or oscillating) veins on the venous side links adjacent venosomes (see Fig. 21.24).

The angiosome concept has several important clinical implications:

1. Each angiosome defines the safe anatomic boundary of tissue in each layer that can be transferred separately or combined on the underlying source vessels as a composite flap (e.g., skin and muscle, muscle and bone, etc). Also, the anatomic territory of each tissue in the adjacent angiosome can usually be captured with safety when it is included in the flap design based on one of the source vessels.
2. Because the junctional zone between adjacent angiosomes usually occurs within muscles of the deep tissue, rather than between them, these muscles provide an important anastomotic detour (bypass shunt) if the main source artery or vein is obstructed.
3. Because most muscles span two or more angiosomes and are supplied from each territory, one is able to capture the skin island from one angiosome by muscle supplied in the adjacent territory. As we shall see later, this fact provides the basis for the design of many musculocutaneous flaps.

The anatomical and clinical territory of a cutaneous perforator

The angiosome concept provides a framework to understand the vascular anatomy of the human body. Plastic surgeons tend to focus on the vascular anatomy of skin but the angiosome concept applies equally to all tissues. The main vascular trunks which supply each angiosome are relatively consistent

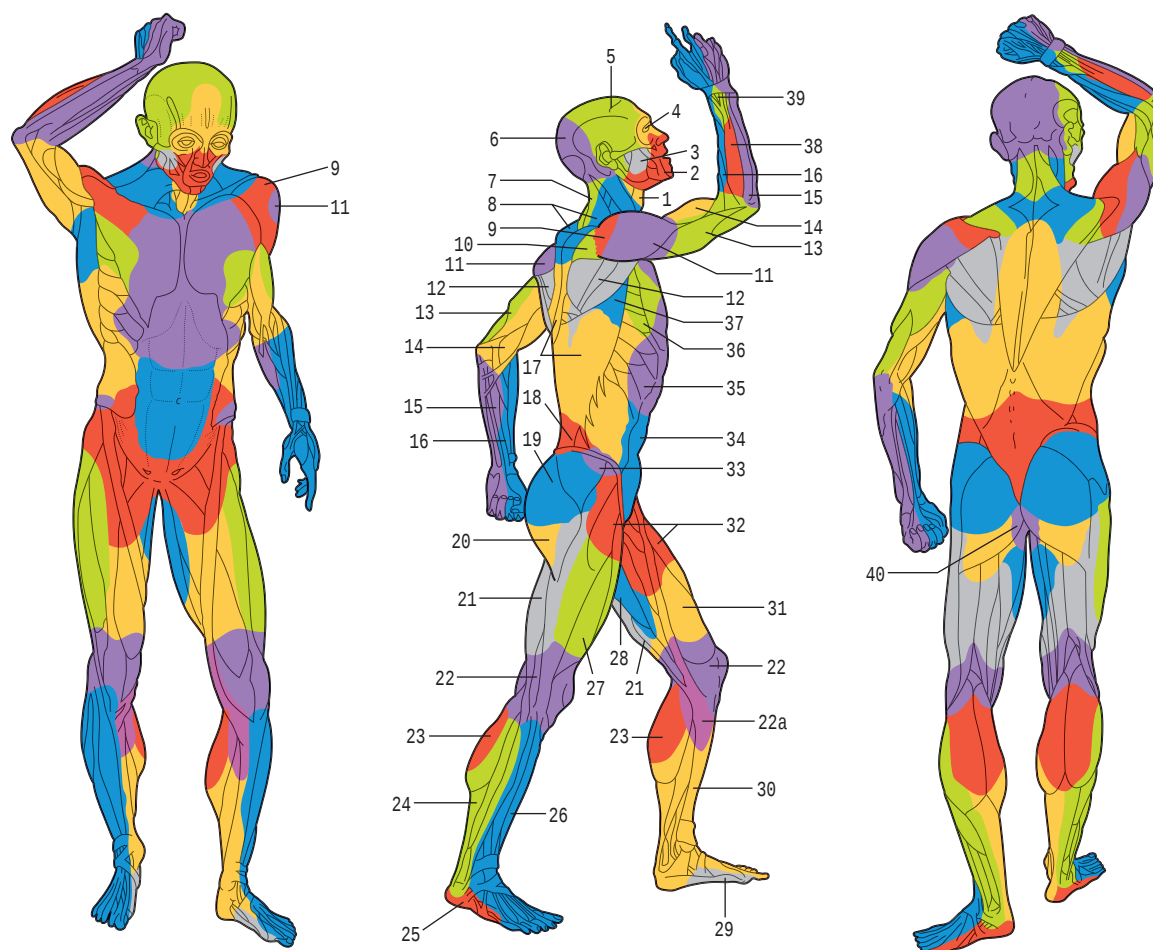


Fig. 21.23 The angiosomes of the source arteries of the body shaded to correspond to Fig. 21.10. The angiosomes are: (1) thyroid; (2) facial; (3) buccal (internal maxillary); (4) ophthalmic; (5) superficial temporal; (6) occipital; (7) deep cervical; (8) transverse cervical; (9) acromiothoracic; (10) suprascapular; (11) posterior circumflex humeral; (12) circumflex scapular; (13) profunda brachii; (14) brachial; (15) ulnar; (16) radial; (17) posterior intercostals; (18) lumbar; (19) superior gluteal; (20) inferior gluteal; (21) profunda femoris; (22) popliteal; (22a) descending genicular (saphenous); (23) sural; (24) peroneal; (25) lateral plantar; (26) anterior tibial; (27) lateral femoral circumflex; (28) adductor (profunda); (29) medial plantar; (30) posterior tibial; (31) superficial femoral; (32) common femoral; (33) deep circumflex iliac; (34) deep inferior epigastric; (35) internal thoracic; (36) lateral thoracic; (37) thoracodorsal; (38) posterior interosseous; (39) anterior interosseous; and (40) internal pudendal.

in size and position, however the individual cutaneous perforators are highly variable in size and position. Each individual cutaneous perforator territory fits together with its neighboring territories like a giant jigsaw puzzle (Fig. 21.25). The arterial connection between adjacent cutaneous perforators may be through reduced caliber choke anastomotic vessels or through vessels which are not reduced in caliber (true anastomoses).⁷⁷ True anastomoses occur variably throughout the body, most commonly along cutaneous nerves or in areas where the skin is mobile.⁷⁸

The importance of true anastomoses relates to the clinical territory of an individual cutaneous perforator. Generally, it has been found in experimental work on a series of animals including pig, dog, guinea pig and rabbit that the limit of viability of a skin flap is related to the anatomy of the pedicle of the flap and the surrounding perforator angiosomes.⁷⁸ Based on the flap perforator, it is possible to reliably capture an adjacent cutaneous territory in any direction. In about 80% of the animal studies, the limit of flap survival was at the junction between second and third territory.

However, if there are true anastomoses between vascular territories, the third territory potentially could be captured based on an individual perforator. This would be analogous to a delay procedure (see Fig. 21.53) in which the choke anastomotic vessels dilate between vascular territories, increasing flap survival. Thus, it is the vascular anatomy of individual perforators and the vascular connections between perforators which govern the survival of flaps based on the perforator. A novel technique using dynamic thermography to preoperatively map cutaneous perforators and their interconnections has been reported which is non-invasive and non-irradiating and shows promise as a tool to predict flap survival.⁷⁹



Access the Vascular Territories of the Body section, including Figs. 21.26–21.38 and Tables 21.2–21.4, online at

<http://www.expertconsult.com>

Vascular territories of the body

The angiosome concept has led to the segregation of the body anatomically into three-dimensional vascular territories. Further work has led to the investigation and detailing of angiosomes in certain parts of the body. Some of these regions are highlighted to expand and to clarify the concept. The description of vascular territories is important to the design of flaps throughout the body.

Vascular territories of the forearm

The forearm is an important flap donor site due to the high incidence of hand and upper extremity injuries around the world.⁵⁰

Forearm skin

The cutaneous perforators arise directly from the source arteries or from their muscular branches, and then they follow the intermuscular septa distally. Proximally, perforators pierce the muscle bellies near where the muscles are fixed at their origins from bone or from the intermuscular septa. The perforators become more numerous but smaller distally, with the maximum number of small perforators being seen in the palm, where the skin is most rigidly fixed. The cutaneous perforators on both the anterior and posterior surfaces of the forearm emerge in rows along the course of the radial and ulnar arteries (Fig. 21.26).

Muscles

In general, muscles are supplied by vascular pedicles from each angiosome that they span. These can be divided into the anterior group and the posterior group.

The anterior group of forearm muscles can be further subdivided into the superficial and deep muscles. The superficial

muscles proximally receive branches from the brachial artery, the ulnar artery, or the ulnar recurrent artery. Distally, they receive branches from the radial artery or ulnar artery (Fig. 21.27).

The deep anterior muscles are supplied by the radial artery, the anterior interosseous artery, and the ulnar artery. Note in Fig. 21.27 that the junctional zone between angiosomes occurs primarily within the muscles and that most muscles span at least two angiosomes.

The posterior group again can be divided into superficial and deep muscles. The superficial muscles receive blood from the radial recurrent artery, which supplies the proximal and lateral halves of their muscle bellies. The distal and medial halves of these muscles receive their blood supply from the posterior interosseous and the interosseous recurrent arteries (Fig. 21.28). The deep muscles receive their blood supply from the radial recurrent artery, interosseous recurrent artery, posterior interosseous artery, and anterior interosseous artery.

When cross-sectional studies of the forearm are reviewed, it becomes clear that the angiosomes of each source artery span between the skin and the bone (Fig. 21.29). It is noteworthy that the proportional representation of each source artery varies between levels in the forearm. Although the angiosome of the anterior interosseous artery does not reach the skin in Fig. 21.29, it eventually surfaces in the distal forearm posteriorly or where the anterior interosseous artery provides a dominant median branch. In the latter case, it supplies the skin on the volar surface.

Forearm bones

The bones of the forearm also conform to the angiosome concept. The radius is supplied mainly by the radial artery by means of several large proximal branches and by very small distal septoperiosteal and musculoepiosteal branches. In the middle, it receives a nutrient branch from the anterior

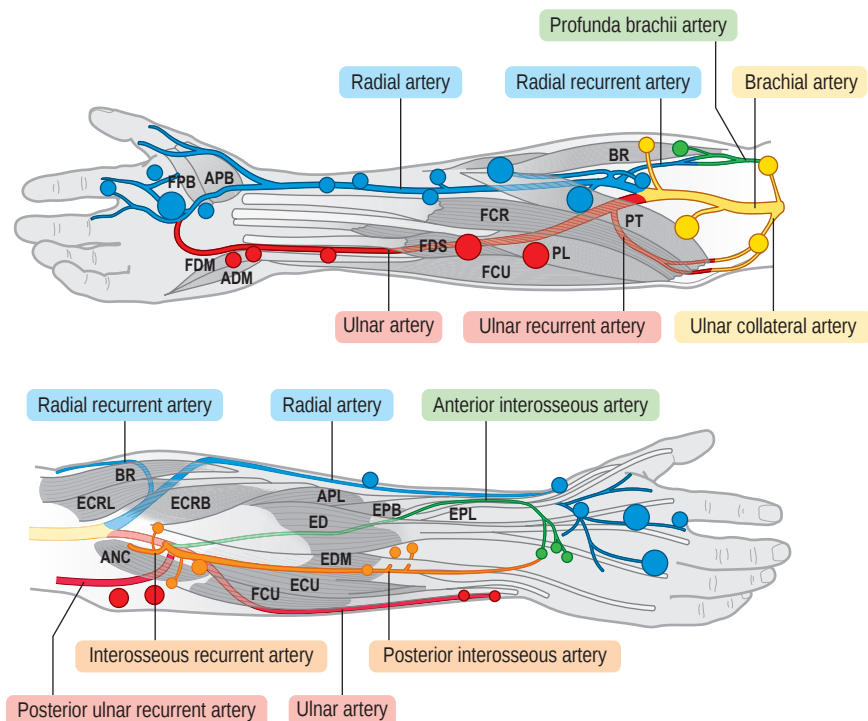


Fig. 21.26 The cutaneous perforators of the forearm, color-coded to match the angiosomes. Large and small skin perforators are indicated by size of the colored markers. Compare with Fig. 21.22. ADM, abductor digiti minimi; ANC, anconeus; APB, abductor pollicis brevis; APL, abductor pollicis longus; BR, brachioradialis; ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; ED, extensor digitorum; EDM, extensor digiti minimi; EPB, extensor pollicis brevis; EPL, extensor pollicis longus; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDM, flexor digiti minimi; FDS, flexor digitorum sublimis; FPB, flexor pollicis brevis; PL, palmaris longus; PT, pronator teres. (From Inoue Y, Taylor GI. *The angiosomes of the forearm: anatomic study and clinical applications*. Plast Reconstr Surg. 1996;98:195.)

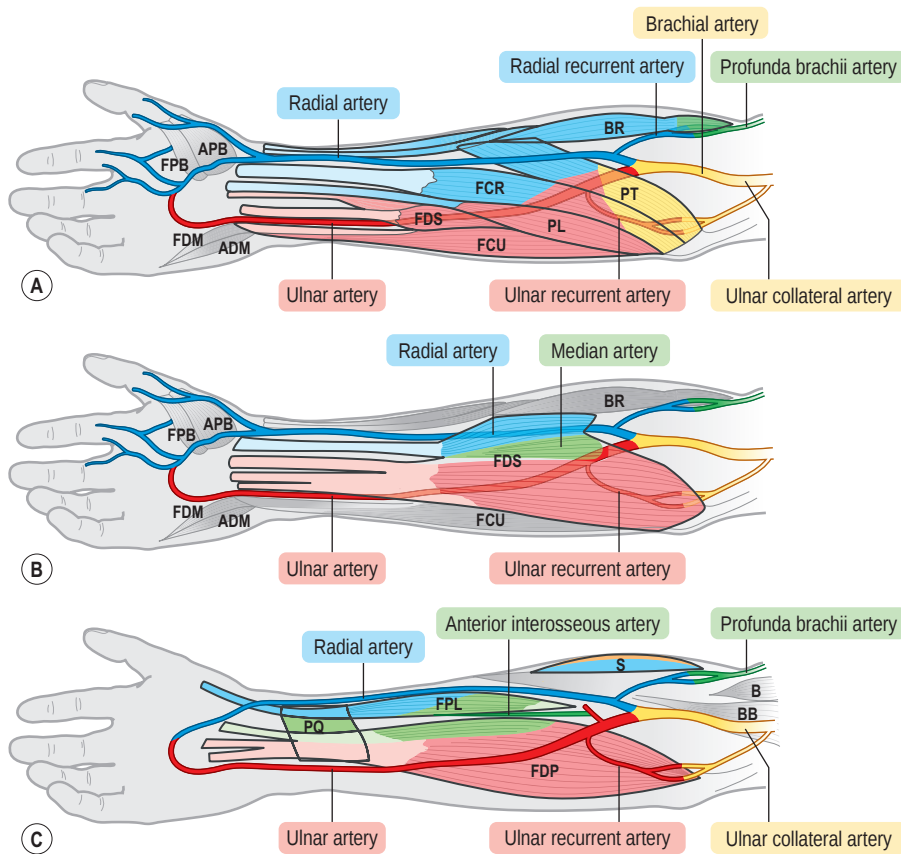


Fig. 21.27 The vascular territories of the (A) superficial, (B) middle, and (C) deep forearm flexor muscles. Note that the junctional zone between angiosomes occurs primarily within the muscles and that most muscles cross at least two angiosomes. Compare with Figs. 21.23 and 21.24. ADM, abductor digiti minimi; APB, abductor pollicis brevis; B, brachialis; BB, biceps brachii; BR, brachioradialis; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDM, flexor digiti minimi; FDP, flexor digitorum profundus; FDS, flexor digitorum sublimis; FPB, flexor pollicis brevis; FPL, flexor pollicis longus; PL, palmaris longus; PQ, pronator quadratus; PT, pronator teres; S, supinator. (From Inoue Y, Taylor GI. *The angiosomes of the forearm: anatomic study and clinical applications*. Plast Reconstr Surg. 1996;98:195.)

interosseous artery. Distally, it also receives one or two small septoperiosteal branches from the anterior interosseous artery, and there is another blood supply from the posterior interosseous artery through the muscles that are attached to the bone.

The ulna is supplied predominantly by the ulnar artery, again through several large proximal and several small distal septoperiosteal branches. In the middle, it receives a nutrient branch from the posterior interosseous artery. Again, as with the radius, another blood supply enters through muscles

attached to the ulna, derived from branches of the anterior interosseous artery.

Clinical implications

Donor site morbidity

From these data, it is evident that the radius and ulna, and nearly every muscle in the forearm, receive a contribution from at least two source arteries. Also, there are intramuscular

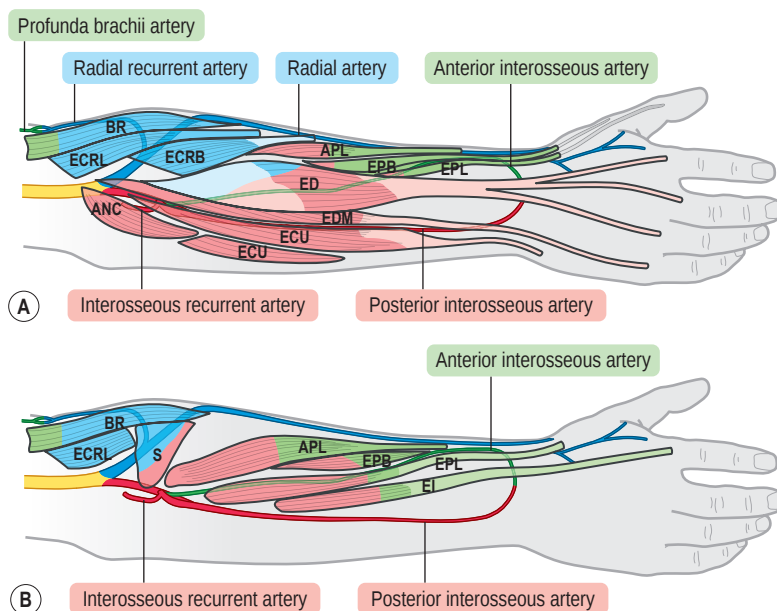


Fig. 21.28 The vascular territories of the (A) superficial and (B) deep forearm extensor muscles, showing once again that the junctional zone lies primarily within the muscles. ANC, anconeus; APL, abductor pollicis longus; BR, brachioradialis; ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; ED, extensor digitorum; EDM, extensor digiti minimi; EI, extensor indicis; EPB, extensor pollicis brevis; EPL, extensor pollicis longus; S, supinator. (From Inoue Y, Taylor GI. *The angiosomes of the forearm: anatomic study and clinical applications*. Plast Reconstr Surg. 1996;98:195.)

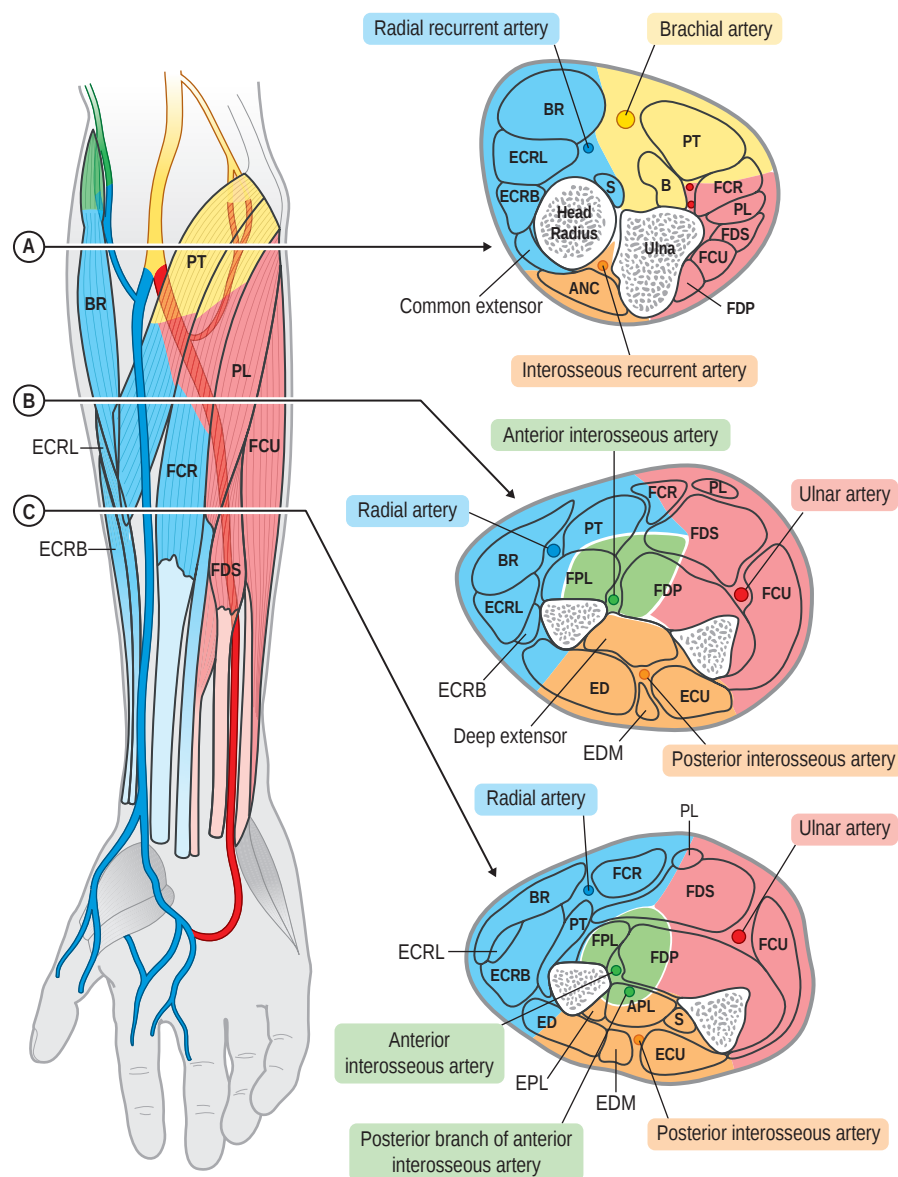


Fig. 21.29 Cross-sectional studies of the forearm at the level of (A) the head of the radius, (B) insertion of the pronator teres, and (C) midforearm, showing the angiosomes of the forearm: brachial (yellow), radial (blue), ulnar (red), anterior interosseous (green), and posterior interosseous (orange) arteries. Note that the junctions of the angiosomes occur within the skin, within the muscles, and within the bone. ANC, anconeus; APL, abductor pollicis longus; B, brachialis; BR, brachioradialis; ECRB, extensor carpi radialis brevis; ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; ED, extensor digitorum; EDM, extensor digiti minimi; EPL, extensor pollicis longus; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; FDS, flexor digitorum sublimis; FPL, flexor pollicis longus; PL, palmaris longus; PT, pronator teres; S, supinator. (From Inoue Y, Taylor GI. *The angiosomes of the forearm: anatomic study and clinical applications*. Plast Reconstr Surg. 1996;98:195.)

and extramuscular anastomoses around the elbow that are usually well developed, especially on the radial side. In addition to the connections within the muscles and skin, particularly well-developed anastomoses occur between vessels that travel on and within the deep and cutaneous nerves.

When the radial artery flap is harvested, the only muscles that lie solely within this angiosome are the brachioradialis, extensor carpi radialis longus, and extensor carpi radialis brevis, supplied by its radial recurrent branch. However, this branch has an excellent anastomosis with the profunda brachii artery. Experience confirms this observation and has shown that dissection of the radial forearm flap can proceed safely right up to the origin of the radial artery from the brachial artery, with either division of its recurrent branch or inclusion of this vessel with one or more of "the mobile mass" muscles.

A proximal dissection of the ulnar artery to its origin from the brachial artery, however, especially if the radial artery is smaller than usual, may lead to problems.

The flexor digitorum profundus and flexor carpi ulnaris are the only muscles supplied solely by the ulnar artery and its

anterior interosseous or recurrent interosseous branches (see Fig. 21.27). If these branches (or the common interosseous artery itself) are divided at their origin while a skin flap is harvested on the ulnar artery, survival of part or all of the flexor carpi ulnaris and flexor digitorum profundus will then rely on: (1) the anastomosis between the ulnar recurrent and the ulnar collateral vessels proximally, an anastomosis that may not be so well developed in some; (2) the anastomosis between branches of the radial artery and the anterior interosseous artery in the midforearm, especially within the flexor pollicis longus; or (3) the connections between the anterior interosseous and a reconstituted posterior interosseous artery in the distal forearm.

In contrast to the flexor digitorum profundus, the flexor digitorum superficialis is better protected because it has an additional contribution from the radial artery angiosome.

Free-flap donor sites

From the angiosome concept, and applying the anatomic knowledge in the previous sections, various tissues can be

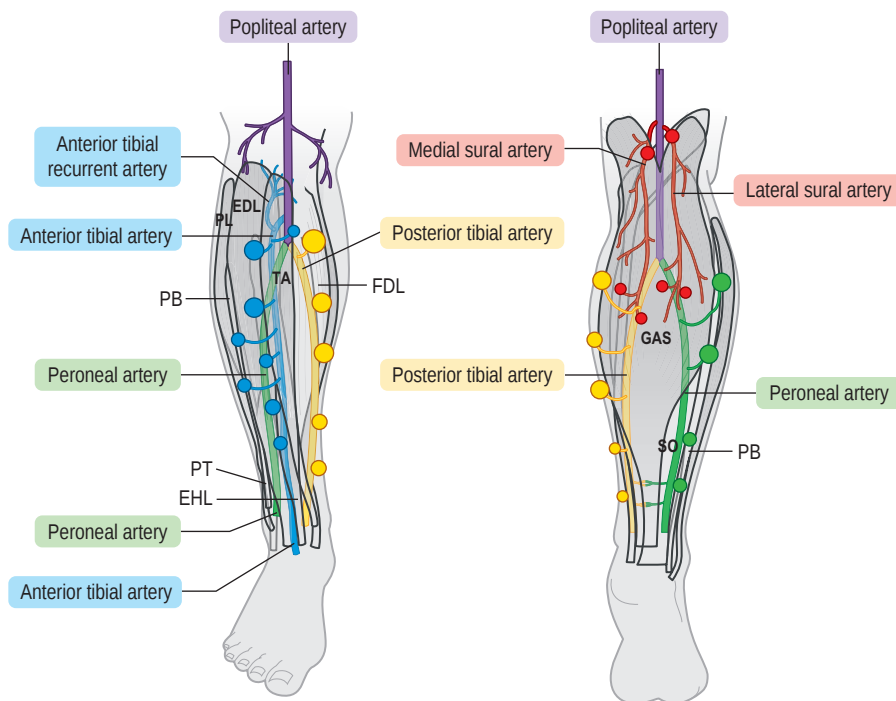


Fig. 21.30 Vascular territories of the lower leg. The colored circles represent cutaneous perforators emerging from the deep fascia and depict relative size of the vessels. EDL, extensor digitorum longus; EHL, extensor hallucis longus; FDL, flexor digitorum longus; GAS, gastrocnemius; PB, peroneus brevis; PL, peroneus longus; PT, peroneus tertius; SO, soleus; TA, tibialis anterior. (From Taylor GI, Pan WR. *The angiosomes of the leg: anatomic study and clinical applications*. Plast Reconstr Surg. 1998;102:599.)

combined or raised separately on the forearm on the various source arteries and their accompanying veins. It has been shown clinically that the dimensions of a flap designed in one angiosome can be extended to include the anatomic territory of the adjacent angiosome in each tissue layer.

In the proximal forearm, the cutaneous blood supply from the radial and particularly the ulnar artery is often musculocutaneous. This is seen especially where muscles are fixed to bone or where they have a common fascial attachment, often before the muscles separate. In these circumstances (e.g., where the muscles arise from the common flexor or common extensor origin), the cutaneous vessels are derived usually from muscle branches and emerge from the muscles near these fixed attachments to bone or fascia.

Vascular territories of the lower leg

In the lower leg, the source arteries and their respective venae comitantes travel adjacent to, but not within, the rigid fascial envelopes of the leg.⁵¹ Here they are invested in loose connective tissue.

Lower leg skin

The cutaneous vessels in the lower leg, as in the forearm, arise from the source arteries or their muscle branches. They pierce the deep fascia in longitudinal rows in the vicinity of the intermuscular septa or beside tendons. They supply branches to each tissue they pass of the lower leg proximally, whether bone, muscle, nerve, fat, tendon, or fascia. There tends to be a line of cutaneous perforators over the anterior tibial, posterior tibial and peroneal vessels. These perforators provide the vascular basis of local perforator or “propeller” flaps for lower leg reconstruction. On the anterior surface proximally, these perforators usually emerge between the tibialis anterior and extensor digitorum longus, where they are derived from the anterior tibial artery, or between the flexor digitorum longus

and soleus muscles, where they arise from the posterior tibial artery (Fig. 21.30). Branches are seen also emerging between the tibia and tibialis anterior muscle and between the extensor digitorum longus and the peroneal muscles, these being derived from the anterior tibial artery. Distally, the vessels appear between the muscle bellies or between the tendons of the extensor digitorum longus, extensor hallucis longus, or peronei, obtaining their supply from the anterior tibial artery. Over the subcutaneous surface of the tibia where the skin is fixed, the deep fascia is continuous with the periosteum of the bone. In this area, branches of the anterior tibial and posterior tibial arteries anastomose freely over the surface of the periosteum.

In the posterior aspect of the leg, vessels pierce the deep fascia around the perimeter of muscles and tendons or from intramuscular septa. On occasion, they have a long intramuscular course and appear as terminal branches of a muscle artery; this is seen especially in the proximal perforators of the peroneal artery.

Lower leg muscles

In the lower leg, a picture similar to that in the forearm is seen, with muscles being supplied by vascular pedicles from each angiosome territory they span.

Anterior leg muscles

The muscles in this compartment are supplied exclusively by the anterior tibial artery (Fig. 21.31). A common vessel frequently passes through one muscle belly to supply the next as well as providing a cutaneous perforator.

This group of muscles is particularly vulnerable to ischemia because they are housed in a compartment with rigid walls across which vascular connections are sparse. This is particularly so medially, where the tibia is subcutaneous. Here the only connections between the anterior tibial and posterior tibial arteries are by means of the periosteum of the bone and

from within the cutaneous network. As can be seen from Table 21.2, all the muscles of this compartment lie in one territory.

Lateral leg muscles

The peroneus longus and peroneus brevis are supplied by the anterior tibial and peroneal arteries, thus forming an important, albeit tenuous, intramuscular connection between their two source arteries (see Fig. 21.31). These muscles are situated within a tight compartment bordered by the fibula, the anterior and posterior intermuscular septa, and the deep fascia. As with the anterior group muscles, the blood supply frequently passes through one peroneal muscle to reach the next, often hugging the fibula during its course.

Table 21.2 Leg muscle angiosomes	
One territory	Tibialis anterior Extensor digitorum longus Extensor hallucis longus Peroneus tertius
Two territories	Peroneus longus Peroneus brevis Flexor digitorum longus Flexor hallucis longus
Three territories	Gastrocnemius Soleus Popliteus Tibialis posterior

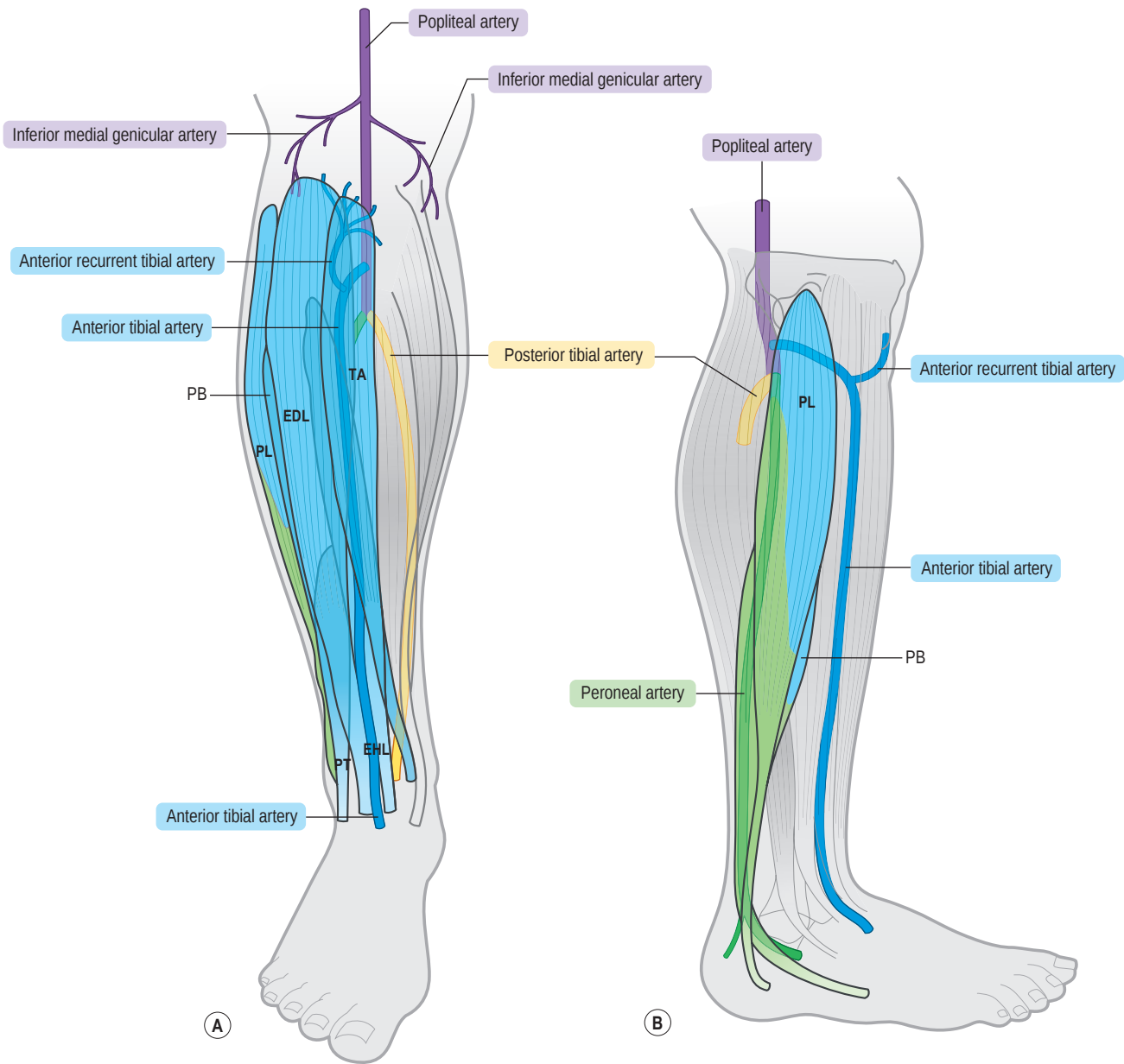


Fig. 21.31 Vascular territories of the lower leg. (A) Illustration of the anterior muscle group that lies totally within the anterior tibial angiosome (blue). This angiosome extends to include part of the peroneal muscles. (B) Illustration of the lateral muscles and their supply from the anterior tibial (blue) and peroneal (green) angiosomes. EDL, extensor digitorum longus; EHL, extensor hallucis longus; PB, peroneus brevis; PL, peroneus longus; PT, peroneus tertius; TA, tibialis anterior. (From Taylor GI, Pan WR. *The angiosomes of the leg: anatomic study and clinical applications*. Plast Reconstr Surg. 1998;102:599.)

Posterior leg muscles

The muscles here can be divided into a superficial group, comprising the gastrocnemius and soleus, and the deep group, comprising the flexor hallucis longus, flexor digitorum longus, tibialis posterior, and popliteus.

The superficial group lies superficial to and is supplied by branches of the popliteal, posterior tibial, and peroneal arteries. Of particular note, blood supply to the gastrocnemius arises proximally in the popliteal fossa from the popliteal artery by the medial and lateral sural arteries to each head of gastrocnemius with little overlap between muscle bellies. This is in marked contrast to soleus, where the blood supply is provided by a large number of short vessels from the posterior tibial, popliteal, and peroneal arteries, which anastomose freely within the muscle, thus forming a vital anastomotic link in the leg.

The deep muscles are supplied by the popliteal artery by means of its inferior genicular branches, the posterior tibial artery, the peroneal artery, and a contribution from the anterior tibial artery (Fig. 21.32).

The junctions between angiosomes, and hence the anastomoses between adjacent source arteries, occur usually within

tissues, especially the muscles, rather than between them (Fig. 21.33).

Leg skin vascular supply

Proximally in the leg, the cutaneous vessels often arise as terminal branches of the muscle arteries and travel to the surface nearby or adjacent to (not within) the intramuscular or intermuscular septa.

In the middle of the leg, the vessels tend to have a more direct course to the skin but again travel close to the septa, either adjacent to or within muscles. As they travel, they usually supply sizable branches to the bones, the muscles, and other tissues.

In the distal part of the leg, the cutaneous vessels have an even more direct course to the skin. However, they still provide branches to the tendons (especially the Achilles tendon), the bones, and the deep fat deposits during their course, a point to be remembered in dissecting the skin paddle of a fibula osteocutaneous flap.

The subcutaneous periosteal surface of the tibia contains anastomoses between the posterior and anterior tibial arteries. Most pretibial lacerations occur superficial to the periosteum

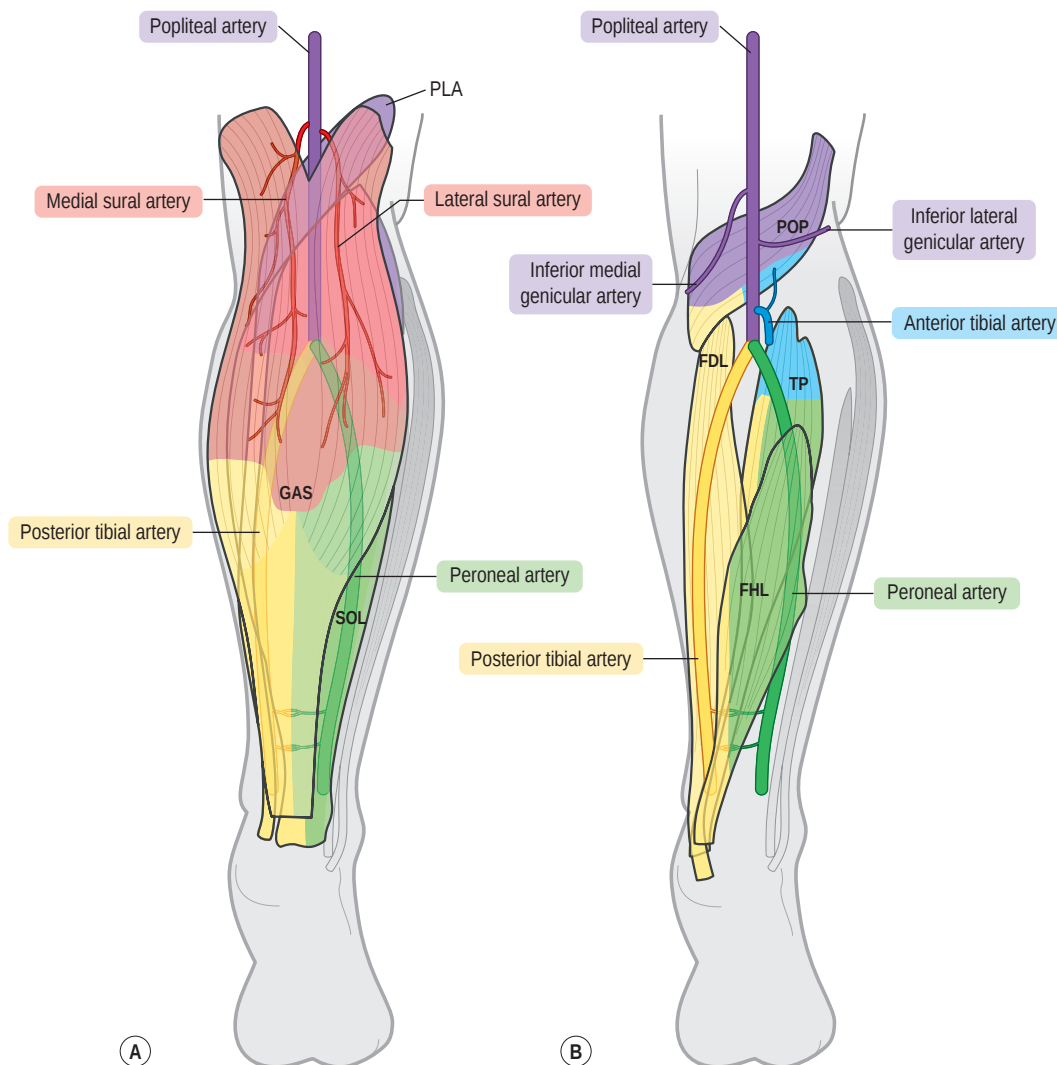


Fig. 21.32 Vascular territories of the lower leg. (A) The superficial muscle group with its supply from the arteries of the popliteal (purple), sural (orange), posterior tibial (yellow), and peroneal (green) angiosomes. All muscles cross at least two angiosomes and receive branches from the source arteries of each. (B) The deep muscles and their supply form the source arteries of each angiosome. FDL, flexor digitorum longus; FHL, flexor hallucis longus; GAS, gastrocnemius; PLA, plantaris; POP, popliteal; SOL, soleus; TP, tibialis posterior. (From Taylor GI, Pan WR. *The angiosomes of the leg: anatomic study and clinical applications*. Plast Reconstr Surg. 1998;102:599.)

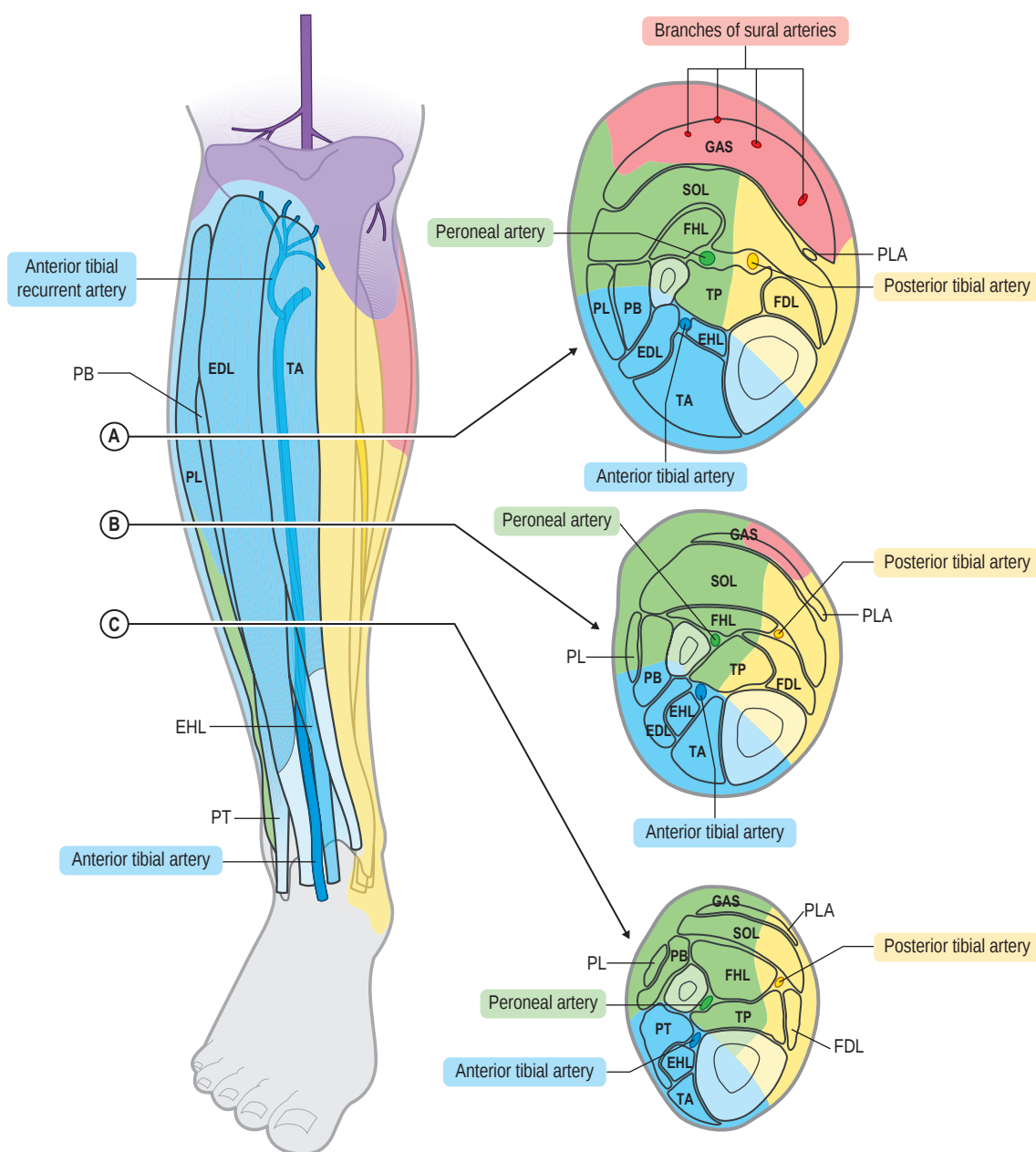


Fig. 21.33 (A–C) Vascular territories of the lower leg. Anterior view of the leg with cross-sections at three levels, viewed distally. The figures show angiosomes of the anterior tibial (blue), posterior tibial (yellow), peroneal (green), and sural (orange) arteries. Note in each case that the angiosome territories extend from the skin to the bone and that their borders, defined by anastomotic vessels, meet usually within tissues, especially the muscles, rather than between them. EDL, extensor digitorum longus; EHL, extensor hallucis longus; FDL, flexor digitorum longus; FHL, flexor hallucis longus; GAS, gastrocnemius; PB, peroneus brevis; PL, peroneus longus; PLA, plantaris; PT, peroneus tertius; SOL, soleus; TA, tibialis anterior; TP, tibialis posterior. (From Taylor GI, Pan WR. *The angiosomes of the leg: anatomic study and clinical applications*. *Plast Reconstr Surg*. 1998;102:599.)

and “shear off” the cutaneous arteries that emerge from this plexus, thus explaining the high incidence of traumatic skin flap necrosis.

Connective tissue framework

The source arteries and their venae comitantes travel adjacent to, but not within, the rigid fascial envelopes that make up the compartments of the leg. They travel in loose connective tissue, usually adjacent to one side of the fascial sheet. This is important surgically, for example, to approach these vessels

to dissect the pedicles of local or free flaps, to use the vessels as recipient sites for transplantation or replantation, or to avoid them in decompressing the leg of a patient with a compartment syndrome.

Compartment syndromes

It seems more than a coincidence that the compartment whose blood supply is anatomically most vulnerable to ischemia, the anterior tibial compartment, is the one most often affected by exercise to give the painful condition of “shin splints”. The

only vessel supplying the muscles of this compartment is the anterior tibial artery with its venous drainage paralleling the arterial supply.

Flap donor sites

Following McGraw and Dibbell's work on the musculocutaneous territories in the leg^{23,25} and Pontén's work,²⁸ which drew attention to the vessels hugging the deep fascia and septa in this region, a large number of flaps have been described based proximally and distally in the leg. In most cases, they have been designed after a review of the anatomy of the leg vessels. Wei *et al.*⁸⁰ have shown that a skin flap can be included with the fibula as a free flap. On review of the cutaneous perforators of the lateral aspect of the leg, it can be seen that the skin paddle should be designed distally in the leg to capture direct septocutaneous perforators from the peroneal artery. Dissection of the distal septocutaneous perforators of the peroneal artery tends to be the most straightforward since the proximal branches tend to have long intramuscular courses.

Vascular anastomoses around the knee

In the previous section on the forearm, emphasis was placed on the anastomoses around the elbow joint. Here, the mass of the brachioradialis, brachialis, and common flexor and extensor muscles plays an important role in bypassing potential obstruction of the brachial artery. The rich intramuscular anastomoses within these muscles between the radial and profunda brachii artery branch laterally, and between the ulnar and ulnar collateral vessels medially, supplementing the extramuscular anastomoses.

Around the knee, the story is very different. Few muscle bellies actually cross the knee joint; most are represented by tendons. The largest of these, the gastrocnemius, has a blood supply that arises in the popliteal fossa, not above it, and has a relatively poor connection with other vessels in the leg. The main anastomoses between the thigh and leg are extramuscular (except for popliteus), represented by the geniculate vessels. This helps explain the observation by Hunter and Salmon^{8,9} that ligation of the popliteal artery, proximal to the sural arteries, has a major effect on the blood supply to the distal leg.

In the popliteal fossa distally, the soleus muscle receives large branches from the popliteal artery, which link the branches of the posterior tibial and peroneal vessels within the muscle substance. This may explain why ligation of the popliteal artery distal to the takeoff of its branches to the soleus at the distal end of the popliteal fossa had little effect on perfusion of the leg, as observed by Salmon.^{8,9}

Vascular territories of the head and neck

The head and neck region is similar to the leg and forearm region in that the angiosomes are connected usually within the tissues, such as muscle, skin, specialized organs, or glands, rather than between the tissues.⁵² The muscles usually have vessels of two or more angiosomes supplying them and in general can be classified into three major groups on the basis of the similarity of their arterial supply (Tables 21.3–21.4). In some areas, the midline anastomoses are rich, especially in the integument of the scalp, forehead, and lips. In other

Table 21.3 Angiosome supply of the head and neck

Muscles of mastication	
One territory	Lateral pterygoid Medial pterygoid
Two territories	Buccinator Temporalis Masseter
Posterior neck muscles	
One territory	Obliquus capitis superior
Two territories	Levator scapulae Rectus capitis posterior major Rectus capitis posterior minor
Three territories	Splenius capitis Splenius cervicis Semispinalis capitis Semispinalis cervicis Obliquus capitis inferior Longissimus cervicis
Four territories	Trapezius
Five territories	Trapezius* Longissimus capitis
Lateral neck muscles	
Two territories	Scalene anterior Scalene medius Scalene posterior
Four territories	Sternocleidomastoid
Anterior neck muscles	
One territory	Thyrohyoid
Two territories	Sternohyoid Longus cervicis Longus capitis
Three territories	Digastric Omohyoid
*Note: Variation in number of angiosomes of trapezius is due to variability in dorsal scapular artery origin.	

regions, such as the tongue and palate, the midline vascular connections – those of the vertebral, lingual, and ascending pharyngeal – are confined to the deep tissues without cutaneous representation.

Head and neck skin and superficial musculoaponeurotic system

The blood supply to the skin of the face, scalp, and neck follows the connective tissue framework. The main skin perforators pierce the deep fascia from fixed skin sites, especially around the base of the skull, around the orbits, around the nostrils, over the parotid gland, along the skin crease lines of the face, and beside the muscles in the neck. They then radiate into mobile skin areas and are intimately associated with the superficial musculoaponeurotic system (SMAS) layer in the face, the platysma in the neck, and the galea in the scalp (Fig. 21.34).

Vascular arcades occur widely in the scalp between the occipital, postauricular, and superficial temporal branches of

Table 21.4 Angiosome supply of the aerodigestive system	
Nose (bilateral)	
Two territories	External nose
Three territories	Internal nose
Tongue and floor of mouth (bilateral)	
Extrinsic	
One territory	Geniohyoid Styloglossus Genioglossus Hyoglossus
Two territories	Mylohyoid Stylopharyngeus
Intrinsic	
Two territories	
Palate, pharynx, esophagus, and trachea (bilateral)	
Five territories exist from hard palate to upper esophagus. There is a paucity of vessels in the midline of the palate	

the external carotid system and the supraorbital, supratrochlear, and dorsal nasal branches of the internal carotid system. The major veins and arteries in the head and neck often run a different course and may be at a distance from each other.

In the neck, the blood supply is more sparse, with the main perforators emerging from their source arteries where the skin is attached (at the anterior border of the trapezius; along the anterior and posterior borders of the sternocleidomastoid; along the hyoid bone superiorly and the clavicle and sternum inferiorly). They form a rich plexus within the platysma muscle anteriorly (the counterpart to the SMAS in the neck) en route to the skin. The external ear is supplied by two angiosomes, the superficial temporal and the posterior auricular (Fig. 21.35).

The external nose has an abundant blood supply from the ophthalmic branch of the internal carotid and the facial branch of the external carotid artery. Classically, the external nasal branch of each ophthalmic artery runs down the dorsum of the nose to anastomose freely with the lateral nasal branch of the facial artery on each side as well as its superior labial branches. In summary, therefore, the external nose, like the external ear, has two angiosomes supplying it on each side

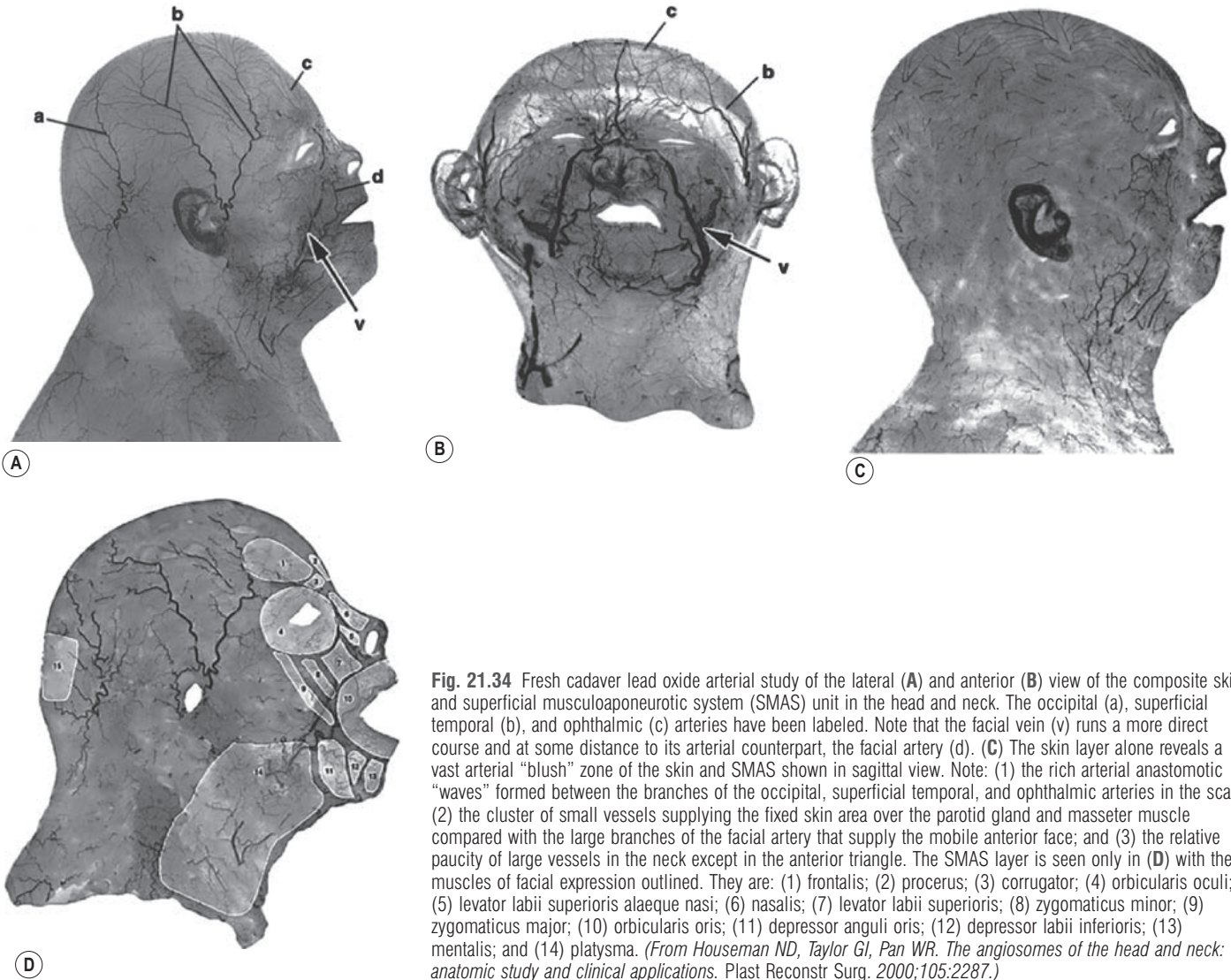


Fig. 21.34 Fresh cadaver lead oxide arterial study of the lateral (A) and anterior (B) view of the composite skin and superficial musculoaponeurotic system (SMAS) unit in the head and neck. The occipital (a), superficial temporal (b), and ophthalmic (c) arteries have been labeled. Note that the facial vein (v) runs a more direct course and at some distance to its arterial counterpart, the facial artery (d). (C) The skin layer alone reveals a vast arterial “blush” zone of the skin and SMAS shown in sagittal view. Note: (1) the rich arterial anastomotic “waves” formed between the branches of the occipital, superficial temporal, and ophthalmic arteries in the scalp; (2) the cluster of small vessels supplying the fixed skin area over the parotid gland and masseter muscle compared with the large branches of the facial artery that supply the mobile anterior face; and (3) the relative paucity of large vessels in the neck except in the anterior triangle. The SMAS layer is seen only in (D) with the muscles of facial expression outlined. They are: (1) frontalis; (2) procerus; (3) corrugator; (4) orbicularis oculi; (5) levator labii superioris alaeque nasi; (6) nasalis; (7) levator labii superioris; (8) zygomaticus minor; (9) zygomaticus major; (10) orbicularis oris; (11) depressor anguli oris; (12) depressor labii inferioris; (13) mentalis; and (14) platysma. (From Houseman ND, Taylor GI, Pan WR. *The angiosomes of the head and neck: anatomic study and clinical applications*. Plast Reconstr Surg. 2000;105:2287.)

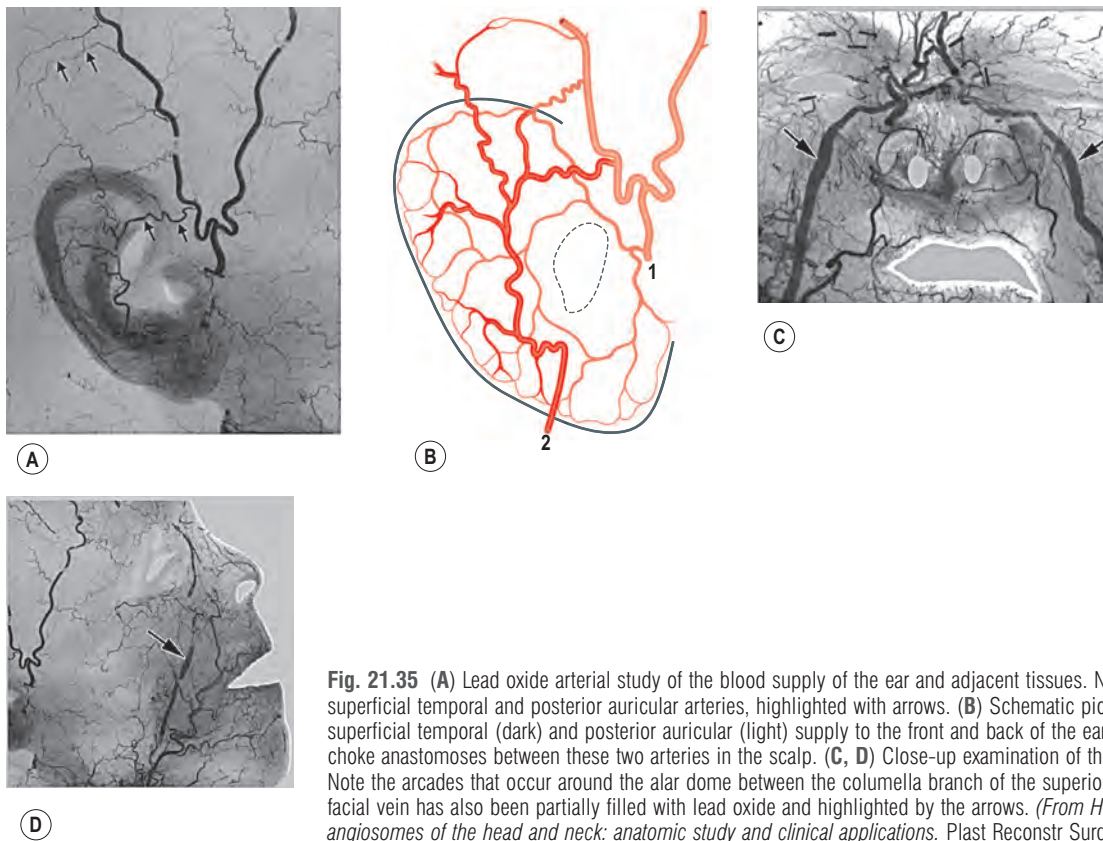


Fig. 21.35 (A) Lead oxide arterial study of the blood supply of the ear and adjacent tissues. Note the arcades formed between the superficial temporal and posterior auricular arteries, highlighted with arrows. (B) Schematic picture shows the branches of the superficial temporal (dark) and posterior auricular (light) supply to the front and back of the ear, respectively. Note also the true and choke anastomoses between these two arteries in the scalp. (C, D) Close-up examination of the arterial anatomy of the external nose. Note the arcades that occur around the alar dome between the columella branch of the superior labial artery and the facial artery. The facial vein has also been partially filled with lead oxide and highlighted by the arrows. (From Houseman ND, Taylor GI, Pan WR. *The angiosomes of the head and neck: anatomic study and clinical applications*. Plast Reconstr Surg. 2000;105:2287.)

and provides a major connection between the internal and external carotid systems (Fig. 21.36; see Fig. 21.34).

The majority of the veins in the head and neck region are avalvular, and most of the valved veins have ostial valves sited at the entry of these bidirectional or oscillating veins into the large collecting directional veins.

Head and neck muscles

The muscles of the head and neck may be grouped according to the number of angiosomes they span and from which they receive a vascular supply (see Table 21.3). These muscles are subgrouped into regions. Together they form an important vascular connection through their intramuscular anastomoses, between branches of the internal carotid, external carotid, and subclavian vessels.

Muscles of facial expression

These muscles lie within the mobile panniculus of the scalp, face, and neck and the aponeurosis of the SMAS. They are intimately related to, are supplied by, and contain within themselves the major branches and cutaneous divisions of the occipital, superficial temporal, ophthalmic, facial, superior thyroid, and inferior thyroid arteries (see Figs. 21.34, 21.36). This whole muscle aponeurotic layer tethered at various points around the skull thus forms a rich continuous anastomotic layer extending from the occiput across the top of the head and face to the root of the neck. Because of the mobility, either the scalp or face, or a combination, can be involved in degloving and scalping injuries. However, because of the rich anastomosis between arteries both longitudinally and transversely across the midline, combined with the poverty of venous valves within their network, successful replantation

of the part without the need for large numbers of vascular anastomoses has been performed.⁸¹

The platysma muscle forms a vascular link between the external carotid and subclavian arteries through its branches of the superior thyroid or submental branch of the facial artery above and the transverse cervical and inferior thyroid

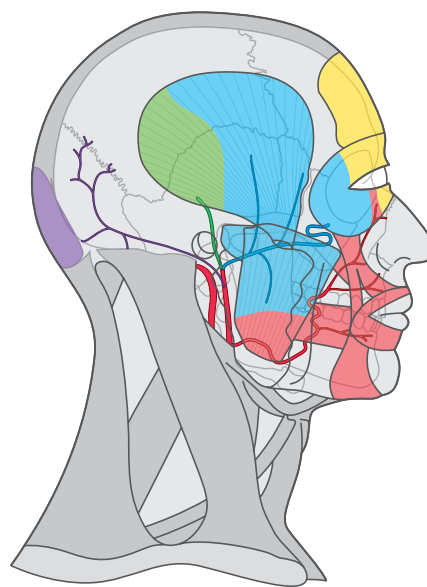


Fig. 21.36 Angiosomes of the muscles of facial expression and mastication in the face. (From Houseman ND, Taylor GI, Pan WR. *The angiosomes of the head and neck: anatomic study and clinical applications*. Plast Reconstr Surg. 2000;105:2287.)

arteries below. As a result, the muscle can be raised on either the superior or inferior pedicle.

The orbicularis oris muscle provides a vascular link between the left and right sides of the face through the facial artery and its superior and inferior labial artery branches. The robustness of this blood supply has been used clinically for more than 100 years in the Abbé flap^{1,82} lip reconstruction.

Ocular muscles

The six ocular muscles all lie within the territory of the ophthalmic artery angiosome. They are therefore potentially vulnerable to ischemia. However, peripherally they are protected by rich anastomoses formed between branches of the ophthalmic artery with (1) branches of the facial artery on the face and (2) branches of the internal maxillary artery in the temporal fossa and the nasal and cranial cavities.

Muscles of mastication

As a group, these muscles cross three angiosome territories, forming a link between the superficial temporal, internal

maxillary, and facial arteries through intramuscular connections (see Fig. 21.36). Buccinator, temporalis, and masseter are supplied by branches from two angiosomes and therefore can be raised on either vascular pedicle.

Posterior neck muscles

As a group, these muscles span and are supplied by up to six angiosome territories. There is thus a staircase of intramuscular vascular anastomoses, especially within the trapezius muscle; between the intercostal branches of the aorta; the suprascapular, transverse cervical, deep cervical, and vertebral branches of the subclavian artery; and the occipital branch of the external carotid artery (Fig. 21.37).

With respect to the trapezius, there is a significant variation in its vascular anatomy, depending on the origin of the dorsal scapular artery.⁸³ This may arise either as a branch of the transverse cervical artery or as a separate branch from the third part of the subclavian artery. As a result, the trapezius has either four or five territories (see Table 21.3).

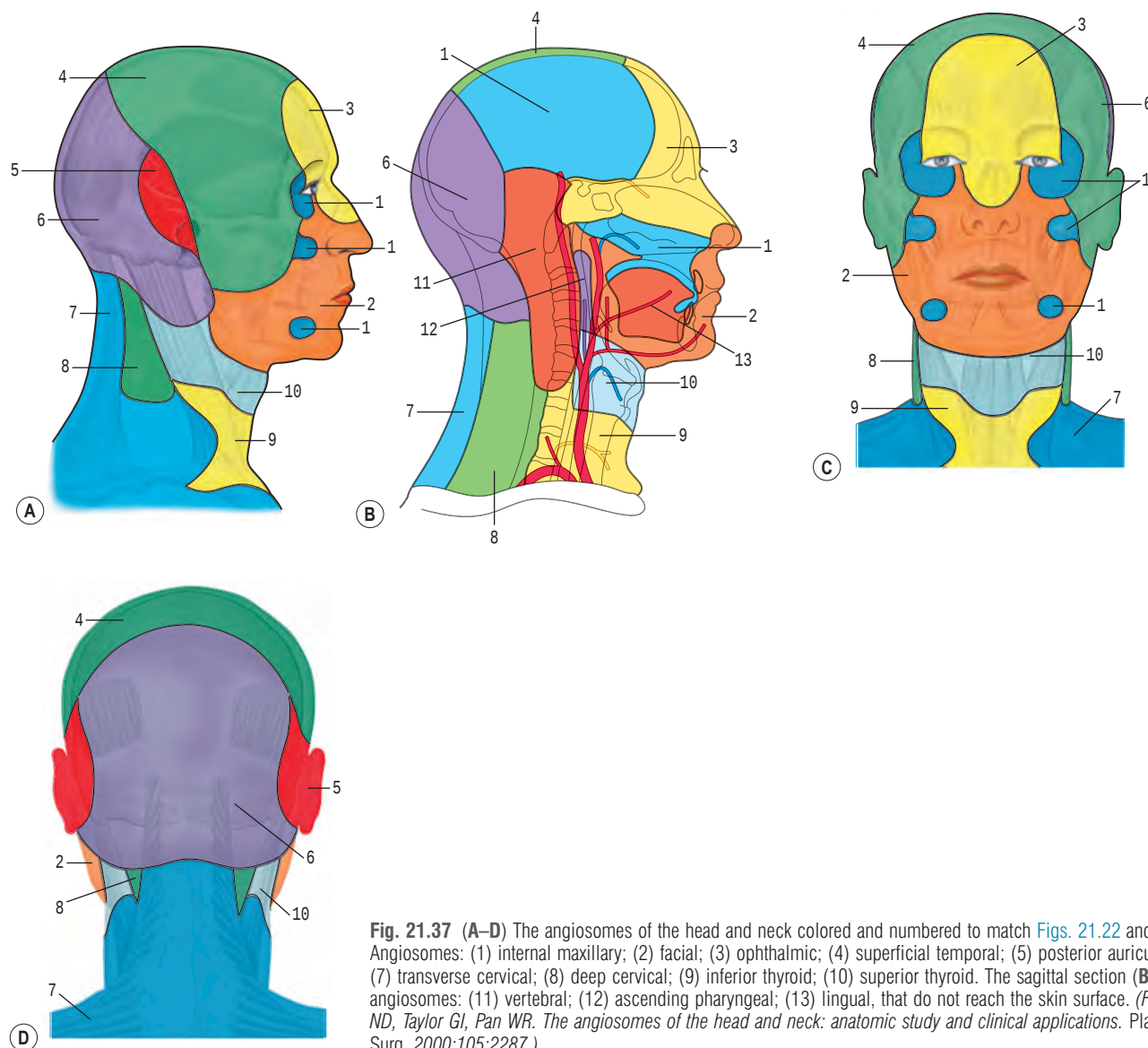


Fig. 21.37 (A–D) The angiosomes of the head and neck colored and numbered to match Figs. 21.22 and 21.35. Angiosomes: (1) internal maxillary; (2) facial; (3) ophthalmic; (4) superficial temporal; (5) posterior auricular; (6) occipital; (7) transverse cervical; (8) deep cervical; (9) inferior thyroid; (10) superior thyroid. The sagittal section (B) shows the three angiosomes: (11) vertebral; (12) ascending pharyngeal; (13) lingual, that do not reach the skin surface. (From Houseman ND, Taylor GI, Pan WR. *The angiosomes of the head and neck: anatomic study and clinical applications*. Plast Reconstr Surg. 2000;105:2287.)

Lateral neck muscles

This group comprises the sternocleidomastoid muscle and the deep scalene muscles. Each spans two or more angiosomes and as a group through intramuscular links provides a pathway between the transverse cervical and inferior thyroid branches of the subclavian artery and the superior thyroid and the occipital branches of the external carotid artery (see Fig. 21.37).

Of note, the sternocleidomastoid has four angiosome territories, the principal two being from the occipital and the superior thyroid arteries. The lower two territories tend to be less dominant, coming from the inferior thyroid and the transverse cervical arteries. In head and neck reconstruction, the sternocleidomastoid muscle has been used for many years. It can be based either superiorly or inferiorly. However, when it is based superiorly, the skin flap located at the lower pole of the muscle has had a high incidence of loss of the skin paddle because of its poor blood supply. This relates to the number of vascular territories that blood from the superior pole must cross to reach the skin paddle. The musculocutaneous flap may be unreliable depending on the vascular supply to the flap and flap design.

Anterior neck muscles

Apart from the small thyrohyoid muscle, which occupies the angiosome territory of the superior thyroid artery, the remainder of these muscles occupy at least two territories (see Table 21.3). These muscles form a link between the occipital, lingual, and facial arteries (see Fig. 21.37).

Aerodigestive system

This system is supplied by no less than seven angiosome territories (see Table 21.4 and Fig. 21.37).

Internal nose

This area is supplied by three primary sources from the ophthalmic, maxillary, and facial artery angiosomes. There are a large number of anastomoses with the blood supply to the external nose (see Fig. 21.37).

Tongue and floor of mouth

The tongue can be divided into extrinsic and intrinsic musculature. The extrinsic muscles are either one-territory or two-territory muscles. Of note, the mylohyoid is supplied on its superficial surface by the submental branch of the facial artery on each side; anastomosis in the midline forms an arterial loop. On its deep surface, it is supplied by the lingual artery and the mylohyoid branch of the internal maxillary artery. The bulk of the intrinsic muscles are supplied by terminal branches of the lingual artery as the vessel enters the posterolateral portion of the tongue on each side. It also receives a small supply from the facial artery. Of note, however, the tongue has an obvious midline raphe, with a poor vascular crossover between the right and left sides (Fig. 21.38). This is of importance in resection of tongue tumors, raising the possibility of tongue tip necrosis on the ipsilateral side if the lingual artery is sacrificed.

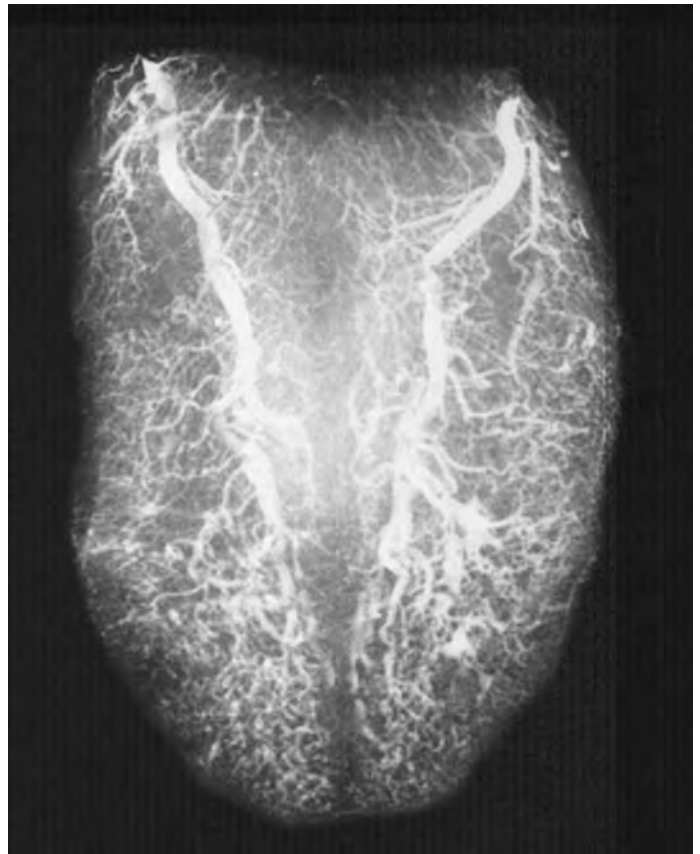


Fig. 21.38 Radiograph of the tongue; note the almost avascular midline. (From Houseman ND, Taylor GI, Pan WR. *The angiosomes of the head and neck: anatomic study and clinical applications*. Plast Reconstr Surg. 2000;105:2287.)

Palate, pharynx, larynx, esophagus, and trachea

The region from the hard palate to the upper portion of the esophagus spans and is supplied by five angiosomes. These comprise the internal maxillary, facial, ascending pharyngeal, superior thyroid, and inferior thyroid arteries. There is a paucity of vessel crossover in the region of the hard palate, and this appears to extend into the pharynx in a fashion similar to the paucity in the midline of the tongue.

Glands

The salivary glands occupy one territory each. The parotid gland receives its supply from the transverse facial branch of the superficial temporal artery as well as a number of smaller branches from the superficial temporal artery.

The submandibular gland is supplied by the facial artery as it runs in the groove between the gland and the mandible. The sublingual gland receives its supply by sublingual branches of the lingual artery.

The thyroid gland spans two angiosome territories on each side, being supplied by the superior and inferior thyroid vessels. These vessels have a rich anastomotic network within each lobe of the thyroid and form an important connection between the subclavian and the external carotid systems on each side and between each side.

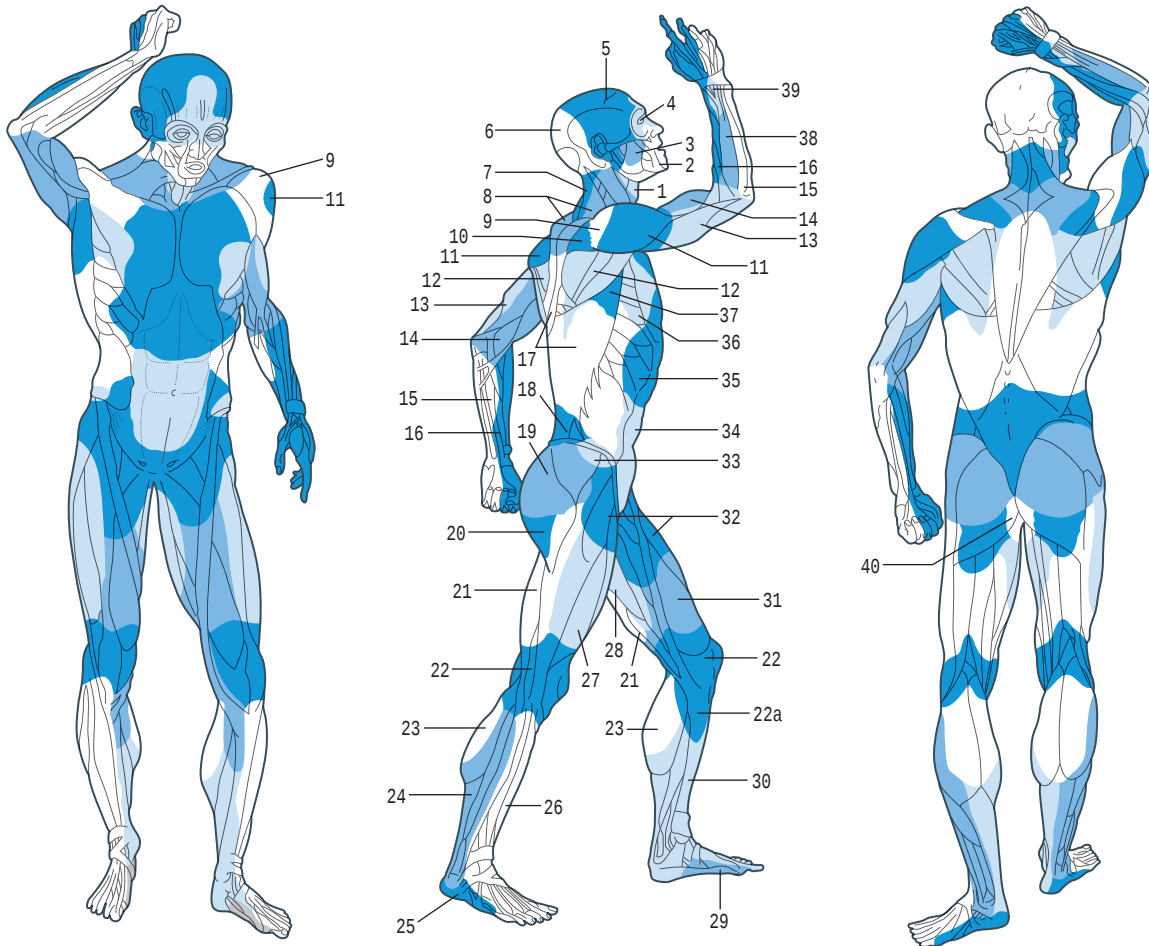


Fig. 21.24 The venosomes of the body. Compare with Fig. 21.22. (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories (venosomes) of the human body: experimental study and clinical implications*. *Plast Reconstr Surg*. 1990;86:185.)

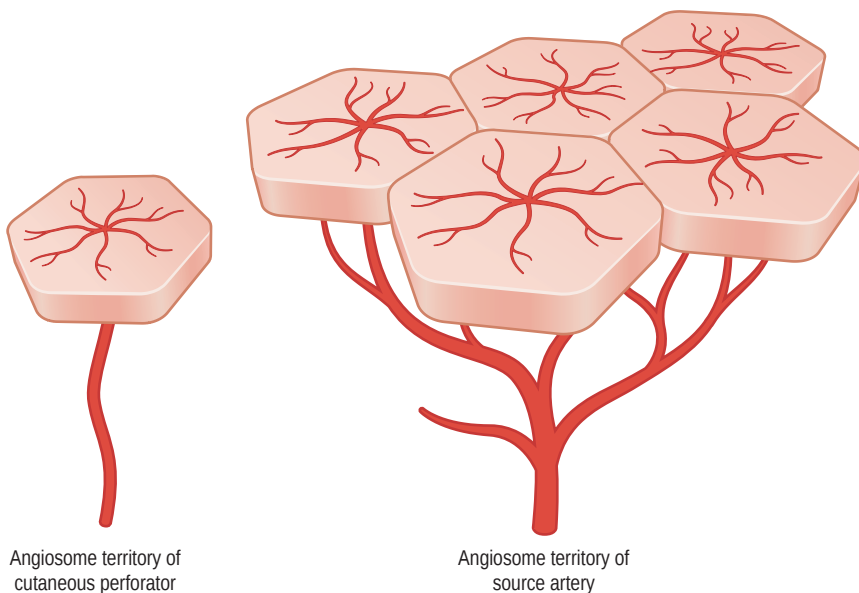


Fig. 21.25 Individual perforator angiosome and relationship between different perforators of a source artery.

Anatomic concepts related to flap design

The following concepts provide an overview of the blood supply to the integument and to the deep tissues (Box 21.1). They are fundamental to the mapping of the vascular territories and to the planning of incisions and flaps. They help explain the anatomic variations that exist between the vessels of different regions of the body and allow better understanding of the various classifications of the cutaneous blood supply that have appeared in the literature. Finally, these anatomic concepts provide the basis for interpreting many physiologic and pathologic processes, including the delay phenomenon and the necrosis line of flaps.

Vessels follow the connective tissue framework of the body

This concept is fundamental to the design of flaps in general and to fasciocutaneous and septocutaneous flaps in particular. The connective tissue framework of the body is a continuous syncytium, like the walls of a honeycomb, calcified in some areas to form the bony skeleton, which houses, permeates, and supports the specialized tissues. The vessels follow this framework down to the microscopic level. Embryologically, vessels develop with connective tissue in the mesoderm and, through development, remain closely related. The clinical application of this is the septocutaneous or fasciocutaneous flap.

In general, if the connective tissue is rigid, such as intermuscular septa, periosteum, or deep fascia, the vessels travel beside or on it. If the connective tissue is loose, they travel within it. The vessels occasionally travel in a fibrous sheath or a bony canal, but this tunnel always contains loose areolar tissue, physiologically, to allow the veins to dilate and the arteries to pulsate.⁸⁴

The pattern is well illustrated if the arterial network is traced from the heart to the periphery. The major arteries are closely related to the bones of the axial skeleton (see Fig. 21.2). Their branches at first follow the intermuscular septa. In the deep tissues, they penetrate the muscles (usually on their

deep surface), tendons, bones, nerves, and deep fat deposits. As the vessels divide and subdivide within the specialized tissues, their branches again follow the connective tissue framework to reflect the architecture of the tissue in question. The arterial framework is beautifully illustrated in the corrosion cast studies of Last and Tompsett (see Fig. 21.2).^{2,85}

The cutaneous perforators exhibit the same pattern. They arise from their source artery (segmental or distributing artery) or one of its muscle branches and follow the intermuscular or intramuscular septa toward the surface (see Fig. 21.8). They pierce the deep fascia, branch, and ramify on its surface and ascend in the connective tissue framework of the superficial fascia, traveling between the fat locules to reach the subdermal plexus. During their course, the cutaneous vessels provide branches to the adjacent tissues, whether they are muscle, nerve, bone, fascia, or fat.

The cutaneous perforating veins can be traced in a retrograde fashion by means of the intermuscular and intramuscular septa to the outer layer of the deep fascia, where they usually form rich plexuses on either side of its surface. From there, they can be followed along the connective tissue framework of the superficial fascia, worming their way between the fat locules until they meet and become continuous with the horizontal plexus of large superficial veins near the dermis.

Arteries radiate from fixed to mobile areas and veins converge from mobile to fixed areas

Few arteries cross mobile tissue planes. Instead, they cross where tissues are anchored and radiate parallel to the plane of mobility, often for long distances. The cutaneous vessels pierce and emerge from the outer layer of the deep fascia near where it is anchored, either to its deep septa or to bone. The overlying integument is fixed also to the deep fascia at these sites. The fixed skin regions are seen easily in a well-muscled individual as grooves and valleys. They can be seen around the perimeter of muscles, especially where they interdigitate; over well-developed intermuscular septa; over the flexor surface of joints; adjacent to the dorsal and ventral midline of the body; around the base of the skull; and in the region of some bone prominences (see Fig. 21.16).

From the grooves and valleys in the deep fascia, the arteries flow toward the convexities of the body surface, branching within the integument. The wider the distance between the concavities and the higher the summit, the longer is the vessel. This pattern is well demonstrated in the blood supply to the integument of the scalp, nose, ears, breasts, and genitalia; the extensor surface of the joints; and the bulging surface of muscles (see Fig. 21.8).

Where the skin is relatively fixed to the deep fascia over a wide area (e.g., in the scalp and many areas of the limbs), the vessels remain close to the surface of the deep fascia for a considerable distance. In the loose skin areas of the body, especially over the pectoralis major muscle, the iliac fossa, and the extensor surface of joints, the vessels course for a short distance adjacent to the deep fascia. Soon they are plastered to the undersurface of the subcutaneous layer by a thin glistening sheet of fascia, and they then pierce the fat obliquely to reach the subdermal plexus, where they travel for long distances.

The veins course parallel to the plane of mobility, often for long distances, and cross where the tissues are anchored to fascia or bone. This is seen at the same site as the arteries.

BOX 21.1 Anatomic concepts

Vessels follow the connective tissue framework of the body

Arteries radiate from fixed to mobile areas and veins converge from mobile to fixed areas

Vessels “hitchhike” with nerves

Vessel size and orientation are the product of tissue growth and differentiation

Vessels interconnect to form a continuous three-dimensional network of vascular arcades

Vessels obey the law of equilibrium

Vessels have a relatively constant destination but may have a variable origin

Venous networks consist of linked valvular and avalvular channels that allow equilibrium of flow and pressure

Muscles are the prime movers of venous return

Within the subdermal plexus and in the subcutaneous fat, the veins and arteries often travel nearby at a distance and only come together when they pierce the outer layer of the deep fascia. Veins leave the subcutaneous tissue and pierce the deep fascia where the integument is anchored to it. This occurs around the perimeter of muscles, in particular where they interdigitate, over well-developed intermuscular septa. This is especially true in the limbs, where they are concentrated in longitudinal rows over the flexor surfaces of joints (e.g., the cubital fossa, axilla, popliteal fossa, and groin); adjacent to the dorsal and ventral midlines of the body; around the base of the skull and orbital margins where the galea is anchored; and where the deep fascia is fixed to bone, such as the subcutaneous border of the tibia (see Fig. 21.10).

In the deep tissues, veins leave muscles usually near their attachments to bone or fascia, most commonly on their deep surfaces. If a group of muscles has a common origin, for example, where the flexor and extensor muscles arise from the epicondyles of the humerus, the venous drainage of each is frequently collected into a large venous arch that courses in the muscle mass close to the bone.

It follows that, where a tissue is mobile over a long distance, whether muscle, skin, tendon, or nerve, large flaps are available for transfer and should be based on the fixed margin or end of that tissue. There are numerous situations in which this observation is used in everyday clinical practice. For example, the large axial skin flaps based on the fixed area of the groin, the paraumbilical region, and the parasternal region use the mobile skin areas over the anterior abdominal and chest walls. The commonly used muscle and tendon transfers are also based on this principle. If mobility exists between tissue planes, this provides a relatively avascular plane.

Vessels “hitchhike” with nerves

There is an intimate relationship between nerves and blood vessels throughout the deep tissues and the skin and subcutaneous tissues of the body, especially where a cutaneous nerve courses on the surface of the deep fascia. An artery may accompany the nerve for a considerable distance, often connecting with its neighbor in chain-link fashion to provide the basis for an axially oriented neurovascular flap. The cutaneous vessels and the nerve are occasionally in juxtaposition; in other situations, they course parallel to each other but at a distance. When the cutaneous nerve crosses a fixed skin site, it frequently “picks up” its next vascular companion (see Figs. 21.15, 21.16).

There are numerous instances throughout the body where this pattern of distribution of nerves and vessels exists to supply the integument. This includes the supraorbital, infraorbital, and occipital neurovascular bundles in the head; the supraclavicular nerves collecting branches of the suprascapular and supraclavicular vessels as they cross the clavicle on to the chest; the intercostal neurovascular bundles on the torso; and the cutaneous nerves of the arm, forearm, thigh, leg, and digits, which are accompanied by long named or unnamed vessels or a chain-linked system of vessels.

The cutaneous nerves are accompanied by a longitudinal system of arteries and veins that are often the dominant blood supply to the region. The veins in company with

the nerves are frequently large venous freeways, such as the cephalic, basilic, long saphenous, and short saphenous systems. The arteries either are long vessels (e.g., the supraorbital, lateral intercostal, or saphenous arteries) or exist as a chain-linked system of cutaneous perforators, often joined in series by true anastomoses without change in caliber (see Fig. 21.16).

The nerves pierce the deep fascia together with the vessels, they emerge separately and cross the vessels at an angle, or they approach the vessels from opposite directions. The main trunk of the vessel or some of its branches peels off to course parallel (see Fig. 21.15) to the nerve. These vessels either course in proximity to the nerve or travel nearby (see Fig. 21.16B).

This neurovascular relationship presents another basis for the design of long flaps with the added potential of providing sensation at the repair site. Many of the current “axial” or “fasciocutaneous” flaps are in fact neurovascular flaps. The original long and short saphenous flaps described by Pontén are examples.

Vessel growth and orientation are products of tissue growth and differentiation

Two centuries ago, John Hunter⁷⁶ suggested that at some stage of fetal development, there are a fixed number of arteries in the body. This has been the authors’ impression in comparing the number of cutaneous perforators encountered while raising the same flap in a child and in an adult. If this concept is correct, it provides a plausible explanation for the density and morphology of the cutaneous arteries in different regions of the body. It explains why vessels radiate from concavities and converge on convexities and why the vessels in some areas are small and close together, whereas in others they are large and spaced well apart (Fig. 21.39 ).

Fig. 21.39 appears online only.

There are numerous examples to support this hypothesis. The sternocleidomastoid and trapezius muscles split from the same somite.⁸⁶ The trapezius “drags” its supplying transverse cervical artery (and nerve) across the root of the neck to the back, together with a large band of skin that it nourishes. Manchot^{4,5} suggested that the long course and the direction of the superior and inferior epigastric arteries are brought about by the extension of the fetal torso. If one remembers that the cutaneous perforators pierce the deep fascia at fixed points and that they all interconnect, this would explain why, as the brain and skull expand, the scalp vessels hypertrophy and are stretched from the base of the calvaria toward its vertex.

The primitive cutaneous perforators in the fetus branch in all directions after piercing the deep fascia and have a stellate appearance. This pattern is retained into adulthood in many regions of the body. When a perforator departs from this pattern and becomes oriented in one direction, it highlights the differential increase in growth that has occurred along that axis or the influence of a developing cutaneous nerve. Where small perforators are clustered close together, this pattern suggests that, by comparison, the growth and hypertrophy in the area are less than at those sites where the perforators are large and spaced well apart. This is well demonstrated by comparing the perforators in the proximal and distal regions of the limbs.

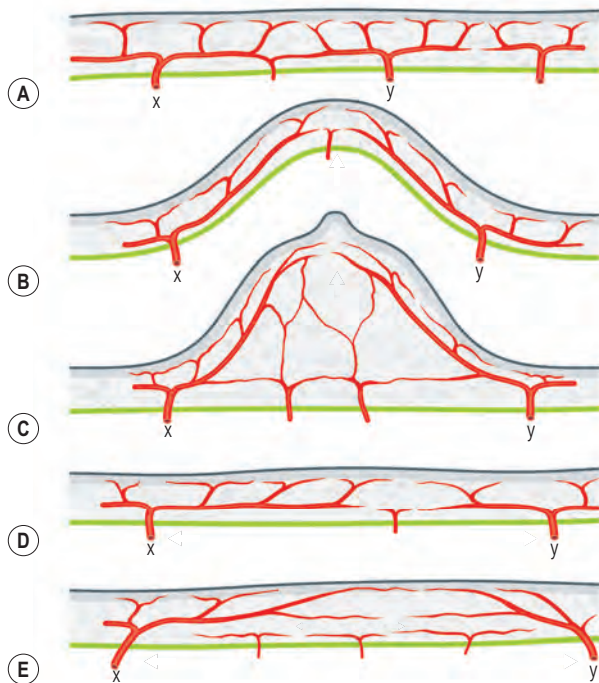


Fig. 21.39 Diagram showing how the size and course of the direct cutaneous perforators x and y, which emerge from fixed points in the deep fascia, could be modified by growth either before or after birth. **(A)** The perforators, which are fixed in number and position, form a major connecting network on the surface of the deep fascia in the "resting state". **(B)** They are stretched with the deep fascia by the expansion of underlying tissues (e.g., the scalp vessels as the brain and skull expand during fetal development). **(C)** As the breast develops within the integument, the vessels are displaced toward the dermis and lengthened as they converge on the nipple. **(D)** They are stretched apart in the limbs as the long bones grow, but they still retain their original relationship to the deep fascia. **(E)** The vessels are again stretched apart by growth, but the mobile relationship between the undersurface of the integument and the deep fascia is responsible for their oblique course. This pattern is characteristic of the loose skin areas of the torso. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

Vessels interconnect to form a continuous three-dimensional network of vascular arcades

Arteries

Throughout the body, each vessel and its branches are connected with adjacent vessels and branches of neighboring vessels to form arches. The keystones in these arcades are formed sometimes by true anastomoses without change in caliber. More commonly, they are represented by reduced-caliber choke arteries and arterioles. The perimeter of choke or anastomotic vessels defines the anatomic territory of each artery (Fig. 21.40). Each vascular territory is surrounded by reduced-caliber choke anastomotic vessels. Thus, each tissue is supplied by a series of linked arterial territories, some small and some large.

Fig. 21.40 appears online only.

The concept is three-dimensional and was documented by Hunter in 1794.⁷⁶ He cited the vascular arcades in the hands and the feet as examples and stated that the arcades are smaller and occur more frequently as the arteries become more distal (Fig. 21.41). Thus, like a Roman aqueduct, the arterial framework consists of tiers of vascular arcades that commence from the aorta and become progressively smaller as the capillary bed is approached. In general, the large arcades are formed by the segmental or distributing source arteries (e.g., the intercostal, radial, ulnar, and deep epigastric arteries) that course between the tissues. Successive tiers of arcades are formed by the arteries, arterioles, and capillaries that supply those tissues.

Figs. 21.41–21.43 appear online only.

Veins

Commencing at the capillary bed, the venous arcades have a design similar to that of the arteries but in reverse, with the tiers

becoming larger and less numerous until the ultimate arcade is reached – the arcade represented by the superior and inferior venae cavae, with the heart situated at the keystone. These arcades link adjacent venous territories in and between tissues.

Within this network, there is a basic venous module that is repeated in the tiers of the venous network, modified in size and shape by the structure and function of the tissue and the embryologic growth and differentiation that have given rise to its adult form (Fig. 21.44A). It is stellate or medusoid in form and consists of a number of collecting veins that converge on a pedicle. A good example of this arrangement is the cartwheel of superficial veins that converge on the saphenous bulb in the groin. In some areas, the tributaries are polarized from one direction, like a tree that has been blown by the wind (Fig. 21.44B); this is true in the scalp, in muscles, and in the leg where the short saphenous vein approaches the popliteal fossa.

The branches within each “venous tree” are linked by channels, often free of valves, that are oriented like the rungs of a ladder or the circumferential loops of a cobweb. These arcades are well demonstrated in the hands, in the feet, in the cubital fossa, and between the venae comitantes that accompany the arteries. Peripherally, the radiating branches of each venous tree are linked to those of its neighbor, again by avalvular veins, to complete the network (Fig. 21.44C). In the integument, large horizontal channels have developed within this reticular framework to subserve the specialized function of thermoregulation (Fig. 21.44D). Their connections with the deep veins are retained as large channels, the venae communicantes, or by means of the smaller venae comitantes of the perforating cutaneous arteries (Fig. 21.45).

Vessels obey the law of equilibrium

This concept was described by Debreuil-Chambardel and is mentioned in Salmon’s description of the cutaneous arteries.^{8,10} Basically, this concept states that “the anatomical territories of

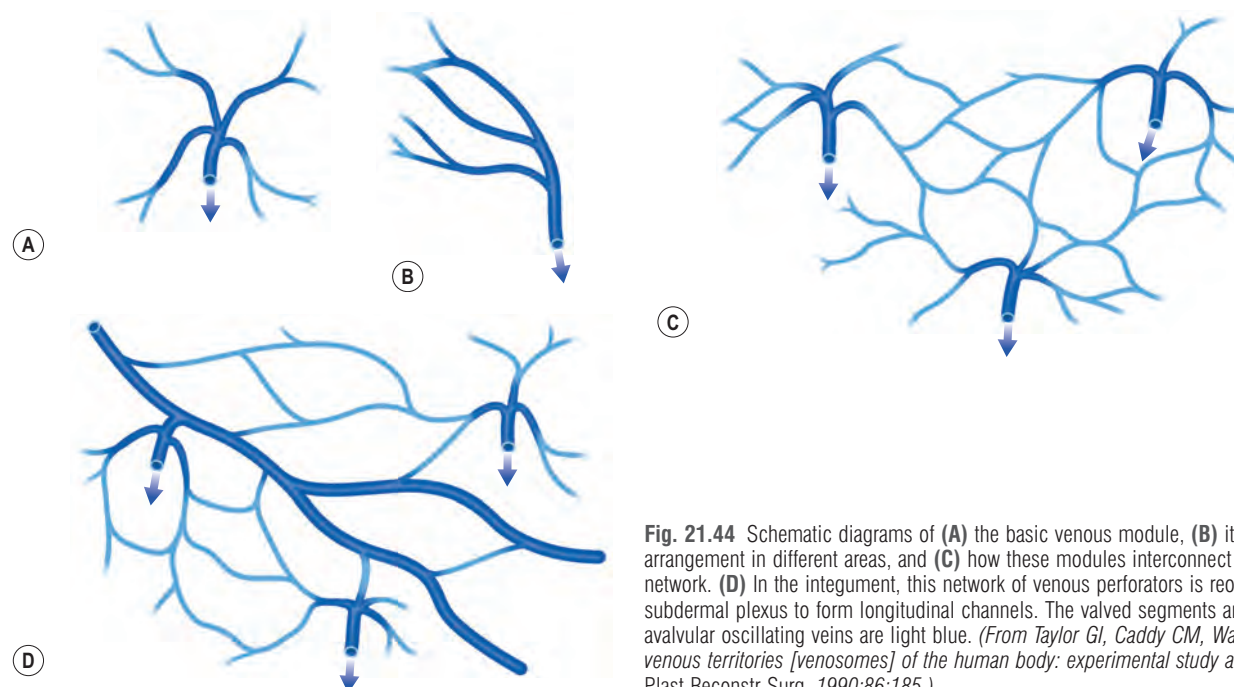


Fig. 21.44 Schematic diagrams of (A) the basic venous module, (B) its modified arrangement in different areas, and (C) how these modules interconnect to form a continuous network. (D) In the integument, this network of venous perforators is reorganized in the subdermal plexus to form longitudinal channels. The valved segments are solid blue, and the avalvular oscillating veins are light blue. (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories [venosomes] of the human body: experimental study and clinical implications.* Plast Reconstr Surg. 1990;86:185.)

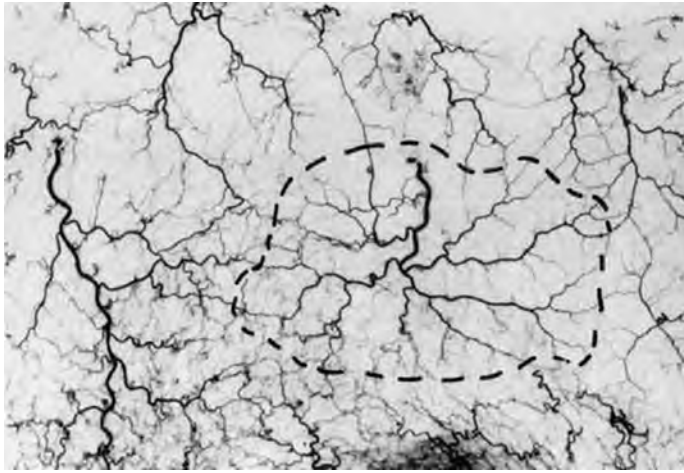


Fig. 21.40 Dotted line through choke connecting vessels of a large acromiothoracic perforator to define its anatomic territory. Compare with Fig. 21.16, left side of chest. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)



Fig. 21.41 Radiographs of the integument of the upper limb and hand. (A) The skin has been incised along the ulnar border. It has been removed (B) with the deep fascia and (C) without it. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

The arterial arcades in the bowel mesentery are a classic example of vascular arcades in the body (Fig. 21.42). The arteries are smaller and more numerous as they approach the intestine. The basic pattern exists in all tissues and is modified by the morphology and function of that tissue. Even during tissue repair, the pattern of vascular arcades is reproduced in granulation tissue. Undoubtedly there are many reasons for the interconnections that exist between arteries, but almost

certainly one of these is to allow the equilibration of pressure across the arcades before the capillary bed is perfused.

Comparison of the vascular architecture in humans with that in other animals and other species reveals a similar arrangement of arcades. In the wings of insects and in the leaves of plants, the veins assume a pattern of interconnecting arcades similar to those of the intestinal mesentery (Fig. 21.43).

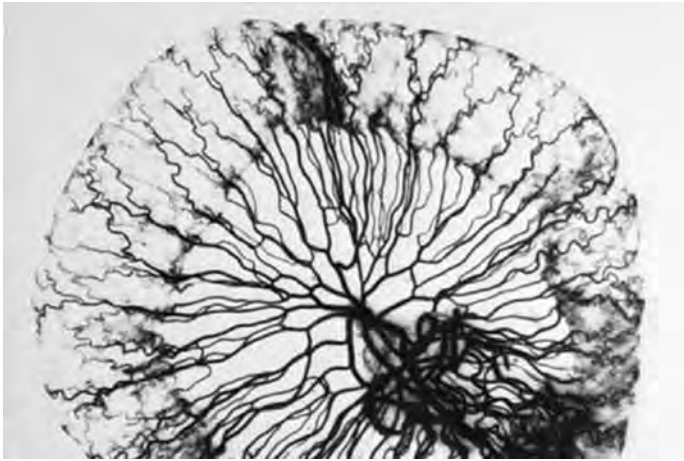


Fig. 21.42 The interconnecting arcades of the small intestine. (From Crosthwaite GL, Taylor GI, Palmer JH. A new radio-opaque injection technique for tissue preservation. *Br J Plast Surg.* 1987;40:497.)

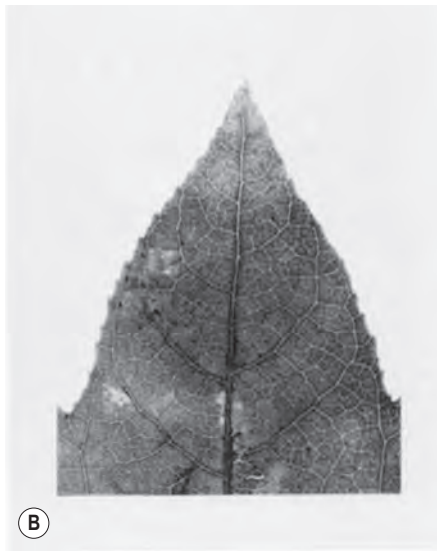


Fig. 21.43 (A) The wing of a moth and (B) the leaf of a tree, showing their interconnecting arcades of “veins”. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications.* *Br J Plast Surg.* 1987;40:113.)

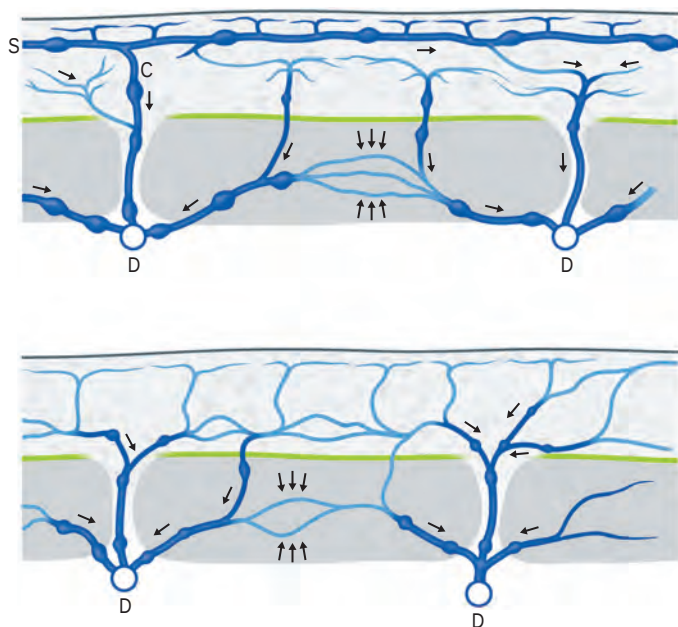


Fig. 21.45 Top: Schematic diagram of the integument and underlying muscle (shaded) in a limb illustrating the superficial (S) and deep (D) venous systems with their interconnecting network. A large vena communis (C) connects these systems, and the alternative pathways of four venae comitantes are shown. The valved veins are dark blue, and the oscillating veins are light blue. Bottom: Similar diagram representing other regions where the predominant venous drainage is by means of the venae comitantes. Note in each diagram that oscillating veins link adjacent territories in the integument and deep tissues. (From Taylor GI, Caddy CM, Watterson PA, et al. *The venous territories [venosomes] of the human body: experimental study and clinical implications*. *Plast Reconstr Surg*. 1990;86:185.)

adjacent arteries bear an inverse relationship to each other yet combine to supply the same region". If one vessel is small, its partner is large to compensate, and vice versa. This is well illustrated by the relative size of the superficial epigastric artery and the perforators of the deep inferior epigastric artery (DIEA). When the superficial inferior epigastric artery territory is noted to be large, the DIEA territory is relatively smaller, and vice versa (see Fig. 21.7). This is an important observation since, if a large superficial inferior epigastric vein is noted, the drainage of the inferior portion of the DIEAP flap may be dependent on the superficial venous drainage system.

Vessels have a relatively constant destination but may have a variable origin

This is typical of the vessels that emanate from the groin to supply the skin of the lower abdomen and upper thigh. The superficial inferior epigastric and the superficial circumflex iliac arteries, for example, may arise either separately from the common femoral artery or as a combined trunk from that vessel or from one of its branches. Whatever the case, their destination is constant to supply the integument of the lower abdomen and the hip (see Figs. 21.7, 21.16).

Venous networks consist of linked valvular and avalvular channels that allow equilibrium of flow and pressure

The venous network of the body is relatively poorly studied, compared to the arterial system. It consists of segments which

have consistent valves and numerous venous channels, large and small, that are free of valves and allow flow within their lumens in either direction. Conversely, there are many small veins that have valves at or near their ostia (sentinel valves) as they enter large channels (see Fig. 21.44).

Directional veins

Directional veins are valved veins which exist either as longitudinal channels, well developed in the subcutaneous and deep tissues of the limbs, or as a stellate pattern of collecting veins, which converge on a pedicle. The cutaneous perforators and the pedicle draining muscles are good examples of the latter arrangement. Because many of their tributaries have valves oriented distally as they converge on the pedicle, they provide the anatomic basis for distally based flaps (see Fig. 21.44).

Oscillating avalvular veins

Oscillating avalvular veins are avalvular vessels which are numerous and may reach large dimensions. They connect and allow free flow between the valved channels of adjacent venous territories, territories whose valves are oriented in the opposite direction (see Figs. 21.44, 21.45). They are also found between the valved channels of the same system; they match and accompany the choke arteries of the arterial framework. In the same way that the choke arteries define the arterial territories, oscillating veins define the perimeter of the venous territories (see Fig. 21.45). This is well illustrated in the study of the muscles (see Fig. 21.14) and in some areas of the integument, especially the torso, head, and neck. In the skin of the limbs, this pattern is overshadowed by the large superficial channels in the subdermal plexus but is apparent in cross-sectional studies. If one mentally subtracts the long, large venous channels from the picture in the limbs, the remaining stellate pattern of the perforating veins matches that of the perforating arteries. It is noteworthy that there is a rich network of large oscillating veins in the anterior thigh. This may provide an explanation for arterialized venous free flaps.

Muscles are prime movers of venous return

Most surgeons have been preoccupied with the arterial supply of the various muscles used for transfer. The efferent veins that accompany the arteries and drain the muscles have been noted and assumed, quite correctly, to be sufficient to provide an adequate venous return.

However, this is but half the picture. There are afferent veins entering almost every muscle in the body that arise from the overlying integument, adjacent muscles, and underlying bone where muscles are attached. When the muscles contract, valves in the efferent veins direct flow toward the heart. During "diastole", valves direct flow into the muscles by means of their afferent veins. If the valves in the muscles in the leg become incompetent (e.g., as the late result of deep venous thrombosis), it would not be difficult to envision the back-pressure effect on the afferent cutaneous veins entering the muscle and their role in the pathogenesis of varicose veins and venous ulceration.

Many veins connect muscle pairs or groups of muscles as arcades. It is noteworthy that the muscles with the richest afferent supply were those that filled most readily with our

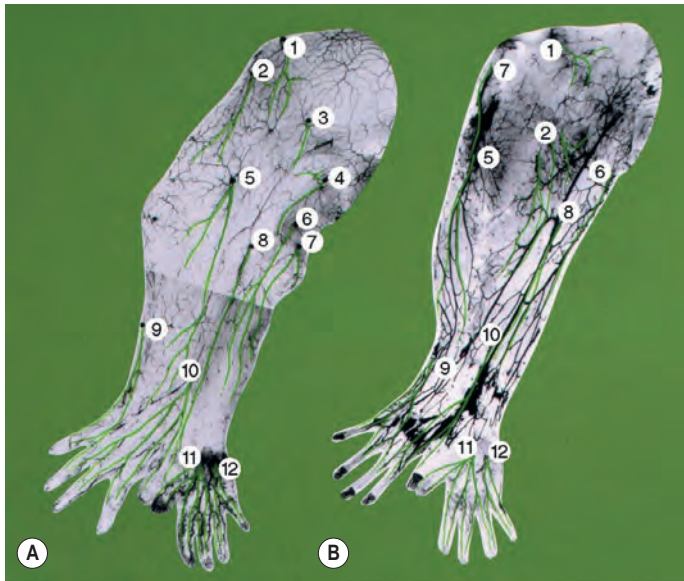


Fig. 21.46 (A) Arterial and (B) venous studies of the integument of the upper limb with: (1) the axillary; (2) lower lateral brachial; (3) supraclavicular; (4) intercostobrachial; (5) posterior antebrachial; (6) medial antebrachial; (7) medial brachial; (8) lateral antebrachial; (9) dorsal branch of ulnar; (10) superficial radial; (11) median; and (12) ulnar nerves labeled. (From Taylor GI, Gianoutsos MP, Morris SF. *The neurovascular territories of the skin and muscles: anatomic study and clinical implications*. Plast Reconstr Surg. 1994;94:1.)

injection studies. Notable examples are the gastrocnemius-soleus complex, the quadriceps muscles, the triceps, and the shoulder girdle muscles, especially the deltoid.

Superficial veins follow nerves and deep veins follow arteries

The venous drainage of the skin following investigation has been found to consist of two parts:

1. A subdermal horizontal network tends to follow the cutaneous nerves. This is seen in the limbs in particular, with named cutaneous nerves following named superficial veins (Fig. 21.46).
2. Where perforating veins pass through the deep fascia in a perpendicular fashion, this occurs with accompanying arteries. As stated in previous concepts, this usually occurs at fixed sites (see Fig. 21.39).

Applications of the angiosome concept

The vascular anatomical information contained in this chapter is an overview to provide the reader with general information important for the design of flaps. From our extensive anatomical studies, we have determined that the general vascular architecture of the body is consistent but variation between different individuals and from side to side in the same individual is the rule. As our understanding of the vascular anatomy of the human body improves, our ability to design and transfer flaps successfully is also improving. Although much is now known about the arterial framework of the body, the venous framework, and the nervous network, there are still gaps in our knowledge. Although knowledge of vascular

anatomy can be applied to all aspects of surgery, the primary focus in plastic and reconstructive surgery is often directed towards successful flap design. Therefore, the clinical applicability of this chapter pertains primarily to the identification of cutaneous perforators, their inclusion in flap design, and augmenting the blood flow of the vessels supplying the flap when necessary.

Preoperative assessment of the cutaneous vascular supply

Flap design

It has been determined clinically and experimentally that flaps can be safely designed by identifying a cutaneous perforator and an adjacent perforator; a line drawn between the two perforators should represent the axis of a viable flap.⁸⁷⁻⁸⁹ In the simplest situations, this approach can work well; however, the technique depends on a very accurate assessment of the cutaneous perforators.

Dopplers

A variety of Doppler ultrasound devices have been utilized to identify cutaneous vessels. The Doppler probe allows surgeons to locate cutaneous perforators with precision in individual cases. Using the knowledge that most cutaneous arteries emerge from fixed skin sites, as already outlined in the section on [anatomic concepts](#) (see Fig. 21.10), their expected origin can be anticipated and located rapidly. The simplest Doppler devices are handheld pencil Doppler probes.⁸⁷ These are easy to use, inexpensive, portable, and provide limited information (Fig. 21.47). All Dopplers require insight into their limitations. Dopplers may pick up background vessels and may not determine the course of vessels accurately. There is considerable inter-observer variability with the use of the Doppler. Obese patients in particular may limit its efficiency for two reasons. First, the thick cutaneous layer may preclude detection of the perforator as it emerges from the deep fascia. Second, as adipose tissue increases, the integument stretches into folds, and the course and destination of the perforators become distorted. However, a simple Doppler is a handy tool to identify cutaneous vessels accurately.

Fig. 21.47 appears online only.

The use of the Doppler probe to locate the origin of cutaneous perforators is not new and has been used by many in the past.⁸⁷ It is not necessary in every case, for obvious reasons. However, its application in free-flap transfer has been found to be invaluable, especially in siting a small flap. A good example of this is the osteocutaneous fibular flap, where just a small skin paddle(s) may be required as a part of the reconstruction. The Doppler probe is a quick, simple method for defining the perforators.

Color duplex Doppler

The more sophisticated Doppler devices are color duplex Dopplers which have greater resolution, cost, and inconvenience but provide much more detail on examination.⁹⁰⁻⁹² The color duplex ultrasound can accurately detect vessel diameter and flow velocity.⁹² Color duplex Doppler has advantages over CTA, including no intravenous contrast, lower cost, and

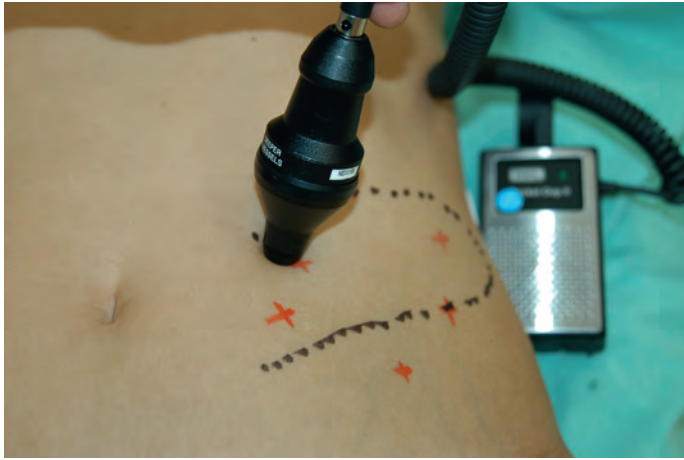


Fig. 21.47 Doppler probe for the design of skin flaps. The handheld Doppler can be used to identify cutaneous perforators for the design of skin flaps. In this case, the Doppler is used to design a flap based on perforators of the deep inferior epigastric vessels.

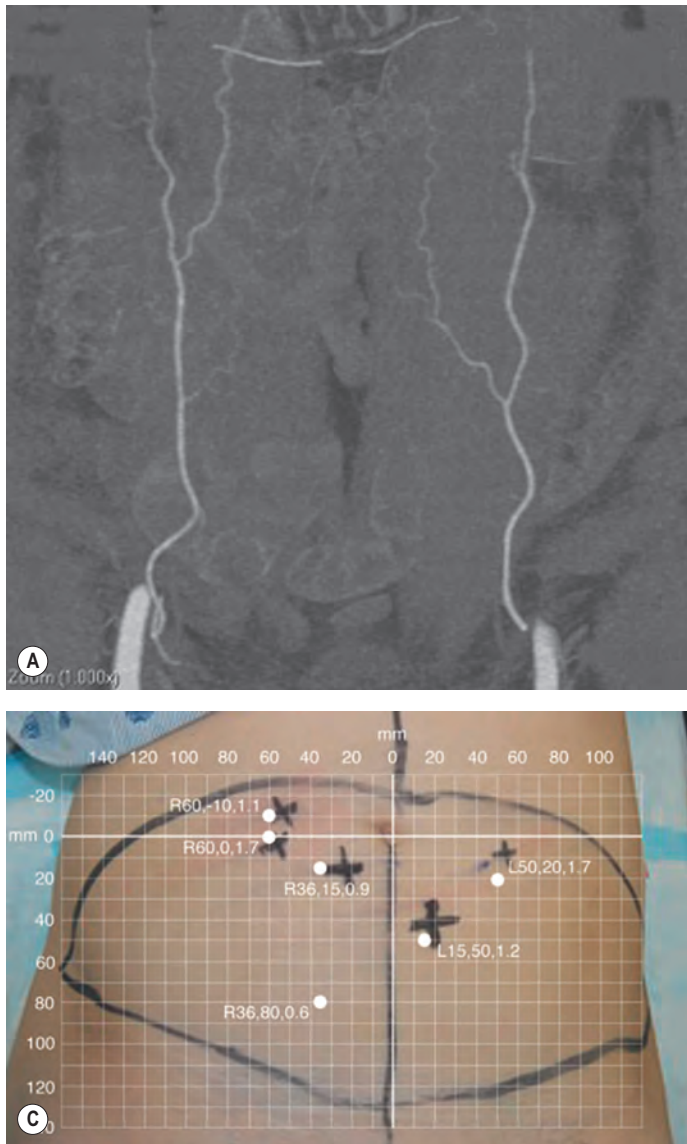


Fig. 21.48 Use of computed tomography angiography (CTA) in the planning of deep inferior epigastric artery perforator flaps. **(A)** Axial view of abdomen in patient preoperatively before deep inferior epigastric artery flap reconstruction of the breast. **(B)** Using CTA to plan surgery. Markings show perforators detected with handheld Doppler. **(C)** Grid overlay with white dots reflects radiologist's description of cutaneous perforators based on CTA using coordinates: R/L, distance from midline in millimeters, distance inferior to umbilicus, size of perforator in millimeters. (From Al-Dhamin A, Berry R, Prasad MA, et al. Coding system for computed tomographic angiography of inferior epigastric artery perforators in DIEAP flaps. *Plast Reconstr Surg.* 2012;129:387e–388e.)

no radiation exposure.⁹² The color duplex Doppler is usually already present in the radiology department of many hospitals but it generally requires training of a technician to obtain reliable and consistent results.

CT angiography

The most accurate method to determine the position, diameter, and course of perforators to the skin is CTA. Masia *et al.* initially reported the use of a multidetector CT scanner to map perforators prior to DIEAP flap harvest.⁹³ The CTA technique has become very popular and is now used around the world to define preoperatively the size, course, and details of individual perforators (Fig. 21.48). We have compared the accuracy of Doppler versus CTA and found CTA to be more accurate and more useful (see Fig. 21.48).⁹⁴ The high-resolution images of CTA provide extensive information for the surgeon regarding individual perforators as small as 0.3 mm.⁹⁵ In DIEAP flap reconstruction of the breast, we have developed a system to report individual perforators using a grid, thus enhancing

communication between radiologist and surgeon (see Fig. 21.48C). Also, in freestyle, perforator free-flap surgery,⁹⁶ knowledge of the perforator course prior to flap harvest can save a great deal of operating room time. The main disadvantages of CTA include cost and radiation exposure. Proponents of CTA highlight the savings gained by reducing operating room time. Also, radiation can be minimized by targeted examinations of the flap donor site. In addition, allergic reactions to contrast dye and claustrophobia are potential patient problems with CTA.⁹²

Axes of skin flaps

The cutaneous arteries of the skin have provided the basis of “axial” flaps used extensively in plastic and reconstructive surgery. Fig. 21.49 shows details of the origin, course, size, density, and interconnections of the cutaneous perforators. It therefore provides for the logical planning of the base and axis of a skin flap. Cross-sectional studies confirm the reason for including the outer layer of the deep fascia with flaps

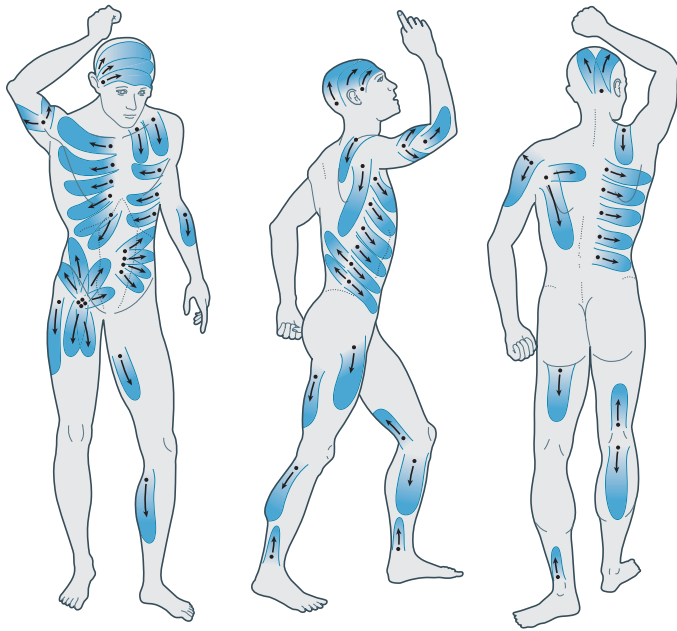


Fig. 21.49 Some of the large axial cutaneous flaps that have been used or are available based on specific perforating arteries and their accompanying perforating veins, as defined by radiographic studies of the integument. In the scalp and the limbs, they should include the deep fascia. Compare with Figs. 21.10 and 21.16. (From Taylor GI, Palmer JH. *The vascular territories [angiosomes] of the body: experimental study and clinical applications*. Br J Plast Surg. 1987;40:113.)

raised in the scalp and in the extremities; in these situations, the vessels hug the fascia for considerable distances. If a flap is designed along the course of the cutaneous nerve, such as the saphenous or the sural nerve, long safe flaps can be and have been elevated. Pontén's²⁸ original flaps were designed in this way, and the saphenous neurovascular flap was planned in a similar manner.⁹⁷ In the loose skin areas of the torso, it is unnecessary to include deep fascia because the cutaneous arteries course at an early stage within the integument. They frequently correspond with the course of the cutaneous nerve.⁹⁸

Distally based skin flaps

Arterial perforators radiate in stellate patterns, and this includes branches that course proximally. The accompanying veins converge from the same directions. Hence, if a flap is based distally over such a perforating system, it will contain arterial branches that radiate proximally from it and valved veins that return to that point. Therefore, it has been noted that the presence of the perforator in the base of the flap is important and allows distally based flaps.^{99–101} An extension of this is the so-called propeller flap (Fig. 21.50), which is a local island fasciocutaneous flap based on a single dissected perforator.¹⁰² The propeller concept is an extension of the perforator flap concept. Basically, the most crucial element to the design of an adequately vascularized flap is the inclusion of a sufficient cutaneous perforator and its corresponding vein in the base of the flap. The flaps can be designed throughout the body in a wide variety of orientations as long as the vessel included as the flap vascular supply is not injured prior to or during the flap elevation and is not kinked. Therefore, gentle tissue handling and surgical technique are important to the success of propeller flaps and other local perforator flaps as well as releasing the deep fascia around the perforator to prevent kinking as the flap is rotated.

Skin flap dimensions

Because the blood supply of the integument, both venous and arterial, has been shown to be a continuous system of linked vascular territories, the survival length of a skin flap must depend on: (1) the caliber and length of the dominant vessels on which the flap is based; (2) the caliber and span of the adjacent captured artery or arteries, vein or veins; (3) the caliber and length of the connecting choke vessels; and (4) an anatomically favorable or unfavorable venous return; and the volume of flap tissue.

Where the arterial perforators are large and widely separated, the territory of each is large and a long flap can be raised with safety. These flaps are characteristic of the loose skin areas of the torso and the scalp. Conversely, if the perforators are small and located close together, the territory of

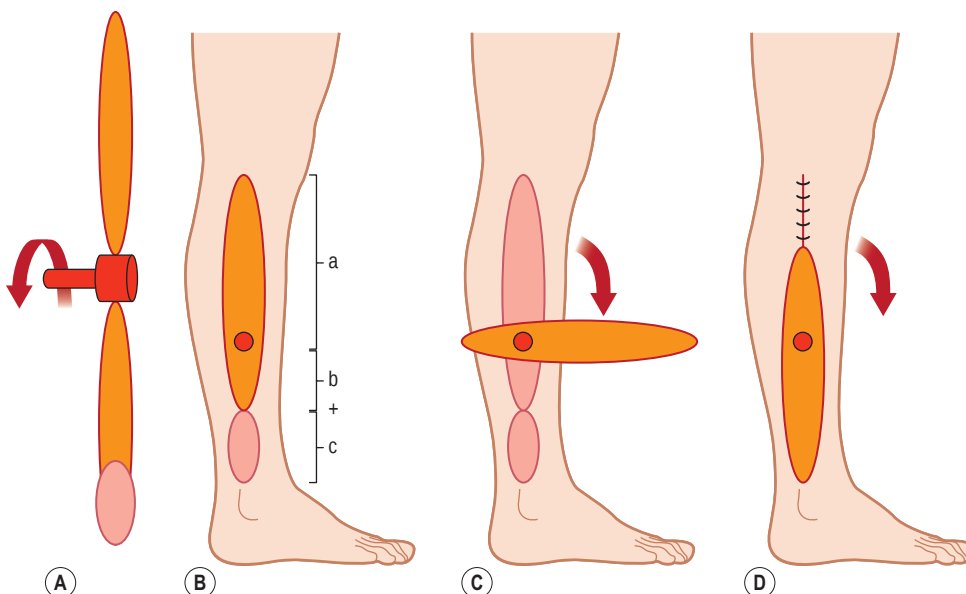


Fig. 21.50 Propeller flap. (A) The flap is likened to the blades of a propeller. (B) The flap is designed based on the largest adjacent uninjured perforator to the wound; $a = b + c + 1$ cm. (C) The flap is elevated based on the perforator. (D) The portion of the flap b is used to cover the donor site and the flap a is used to cover the wound. (From Teo TW. *The propeller flap concept*. Clin Plast Surg. 2010;37:615–626.)

each is small. The viable length of the flap is short unless the supplying source vessel is included in the design. This is evident in the fixed skin area of the sole of the foot.

If very large flaps are required or if vessels of a large caliber are necessary for microvascular anastomoses, the requirements can be satisfied by dissecting the perforators through the intermuscular septa or the intramuscular septa to include the underlying source vessels. The intelligent use of a delay also allows safe capture of adjacent vascular territories.

When we consider the venous drainage, the large longitudinal veins in the subcutaneous tissue of the limbs offer excellent venous drainage for proximally based flaps because their valves are oriented in that direction. However, in the lower abdomen, the drainage of proximally based flaps may be anatomically unfavorable because the valves of the superficial inferior epigastric veins are directed distally toward the groin. The undermined flap of a transverse abdominal lipectomy is a case in point, and perhaps fortuitously, the area of the flap in question is resected in the procedure.

The scalp veins are mostly free of valves, and hence flaps based in any direction will drain favorably. In many regions, however, the venous network consists of territories of valved veins oriented in different directions that are linked by oscillating veins.

The precise mechanism of the necrosis line of a flap is unknown, although the opening-up of arteriovenous shunts provides a plausible theory. Whatever happens, it has been shown that the choke vessels on the arterial side and some of the valved territories of the venous return provide a potential mechanical obstruction to flow.

Fasciocutaneous flaps

The deep fascia should be included in the design of the fasciocutaneous flap in those sites where the skin is relatively fixed to the deep fascia, for example, in the limbs or the scalp. In these instances, the dominant cutaneous vessels course on or lie adjacent to the deep fascia. Although they can be dissected free in some cases, it may be simpler and safer to include the deep fascia with the flap. However, where the skin and subcutaneous tissues are mobile over the deep fascia, for example, in the iliac fossae or the breast, it is unnecessary to include this fascial layer because the major cutaneous vessels have already left its surface. To some extent, the initial enthusiasm for fasciocutaneous flaps has been tempered by increased anatomical understanding and there are relatively few indications for the inclusion of deep fascia in a cutaneous flap.

The term “septocutaneous” is sometimes misleading, especially when it is used to describe a surgically created entity rather than a true anatomic structure. This may occur, for example, where the cutaneous perforators of a radial or ulnar flap are dissected within an envelope of loose areolar tissue. Furthermore, the septocutaneous flap may provide traps for the unwary surgeon. In some cases, the cutaneous artery and its accompanying vein leave the underlying source vessels and course toward the surface in a surgically favorable position, adjacent to a true white fibrous intermuscular septum. This is typical of the blood supply to the skin of the lateral arm flap, where cutaneous perforators arise from descending branches of the profunda brachii vessels and follow the lateral intermuscular septum toward the skin. This

pattern of supply usually exists where the muscles glide on either side of the intermuscular septum.

However, if the muscles attach to either side of the intermuscular septum, the cutaneous perforator may have a variable course. This variability is seen in particular in the lateral aspect of the upper calf. If a compound skin and bone flap is designed at this site over the lateral intermuscular septum based on the cutaneous perforators of the peroneal vessels, either these skin vessels may course directly to the surface, traveling in a favorable position, either adjacent to the septum or within the substance of the soleus or flexor hallucis longus muscles, close to their attachments to the fibula, or alternatively, they may arise indirectly from branches to the soleus or flexor hallucis muscles as terminal twigs of muscle branches that have arisen from the peroneal vessels at considerable distance from the lateral intermuscular septum. In these cases, a long and laborious intramuscular dissection of the cutaneous supply will be required to raise the flap successfully.

Musculocutaneous flaps

The musculocutaneous flap initially became popular when it was recognized that the large vessels supplying muscle were more reliable than the much smaller cutaneous vessels, and as a result the skin overlying the muscle was reliably transferred.^{23–26} Musculocutaneous flaps remain preferable in cases where large vascularized tissue bulk is required. However, it is now understood that the musculocutaneous perforators can be harvested without the bulk of the muscle as perforator flaps. When skin and deep fascia are firmly bound to the underlying muscle (e.g., the gluteus maximus and latissimus dorsi), the blood supply to the overlying skin is ensured. At each fixed site over the muscle, vessels emerge to supply the integument. However, when the muscle is mobile beneath the deep fascia (e.g., the gracilis muscle), the cutaneous supply is at most tenuous.

In general, musculocutaneous flaps can be raised safely if the skin paddle is placed over the perforators of the feeding muscle artery or those in the adjacent muscle territory. Attempts to capture territories beyond this, without previous delay, frequently result in vascular insufficiency. This situation may prevail, for reasons already outlined, in the pectoralis major and the pedicled TRAM flaps.

Depending on the muscle type and the site of the skin paddle, the venous pathway once again may become anatomically favorable or unfavorable. In each case, the venous drainage is thrust on perforators that drain to the intramuscular plexus of veins. In type I muscles, the drainage is favorable regardless of the site of the skin paddle over the muscle because the venous drainage is in one direction. If the skin paddle is placed over the distal territory of type II and type III muscles, the valves of this territory are oriented in the opposite direction to those of the draining pedicle, and the pathway is anatomically unfavorable. This problem was highlighted by Costa *et al.*¹⁰³ in their investigations of the venous drainage of the pedicled TRAM flap.

Many of the musculocutaneous flaps are being replaced by local or free microvascular perforator flaps based on the musculocutaneous perforators. These musculocutaneous perforators are variable in size and position and require a flexible operative approach. These “perforator flaps” are used

to provide large vessels for microvascular transfer; to eliminate the bulk of muscle, when appropriate; and to preserve muscle function, for example, in harvesting a lower transverse abdominal skin flap on one or more perforators of the deep inferior epigastric artery flap.^{38,39}

However, all cutaneous flaps are based on cutaneous perforators, whether direct or indirect, and regardless of whether they pass between or through the muscles to reach the overlying integument. Hence, to confine the term “perforator flap” to those instances in which the cutaneous vessel emerges from muscle to perforate the overlying deep fascia is misleading. The term “perforator flap” therefore should include any island skin flap, based on a cutaneous perforator, whether it arises from a source vessel between or within a muscle or other deep tissue. Some of the early free flaps, for example, the groin flap, are true perforator flaps, in this instance based on the superficial circumflex iliac or superficial inferior epigastric artery.²²

Perforator flaps

A perforator flap has been variously defined as a cutaneous flap based on a musculocutaneous perforator or any cutaneous flap based on any vessel supplying the skin.^{30,104–106} However, this is a semantic discussion which is not as important as the concept of perforator flaps, which represent the continuing evolution of tissue transfers. Initial pioneering reports of perforator flaps demonstrated that it was possible to harvest a skin flap reliably based on musculocutaneous perforators.^{38,107,108} Perforator flaps have the advantage of the large vessel size of vessels supplying muscles of the body without the disadvantages of unnecessary muscle bulk and the loss of function of unnecessary muscle sacrifice. The popularity of perforator flaps has increased exponentially, as evidenced by publications in the world’s plastic surgery literature, since the initial reports of this surgical technique.

Anatomical understanding has laid the groundwork for the success of perforator flaps.⁴⁷ Without detailed knowledge of the underlying vasculature, perforator flap surgery would be difficult. We have compiled an atlas of the perforators of the human body and subdivided their distribution into 61 vascular territories (Fig. 21.51).^{39,40,109} There are approximately 400 cutaneous perforators to the skin, about 60% musculocutaneous and 40% septocutaneous.^{39,40,109} The field has opened up significantly due to increased enthusiasm of surgeons to learn the “perforator flap technique” and increased flap options. Ultimately, perforator flaps have become more popular because patient outcomes have improved. Moreover, the emphasis on perforator flaps has focused attention on the vascular anatomy of the skin. Many of the 400 perforators to the skin can be used as a local or free-flap vascular supply, thus expanding the possible flap options dramatically. The use of the perforator flap technique allows clever and customized reconstructions which can provide optimal patient outcomes. However, perforator flaps are simply more flaps in the armamentarium of the plastic surgeon and good clinical judgment is still required to choose the best flap or technique for a specific application.¹¹⁰

The early pioneers of perforator flaps named flaps in a descriptive fashion which led to a wide array of terms to describe the flaps.^{104,110} In some cases, several terms were used for the same flap, which led to confusion and sometimes

delayed meaningful communication about the flaps.^{104,110} In an effort to standardize descriptions of perforator flaps, we introduced a nomenclature in which all perforator flaps are named according to the source vessel supplying the flap.³⁰ The letters AP are added to indicate artery perforator and the initials of the muscle through which the perforators travel are added as a suffix (Fig. 21.52). Hence, in the case of a DIEAP flap, DIEAP-ra (rectus abdominis). The suffix with muscle initials is only necessary when the perforating vessels can pass through different muscles. The suffix -s indicates that the perforator flap is a septocutaneous flap.

The choice of a suitable perforator and the dissection of the pedicle of a musculocutaneous perforator flap through a muscle require training, expertise, and gentle operative skills. Generally, the perforator flap is planned preoperatively using a handheld Doppler, a color duplex Doppler, or CTA.^{92,111} The largest perforator is usually chosen for the flap. As the flap dissection begins, each perforator over 0.5 mm in diameter is preserved until the pedicle is clearly visualized. As the dissection proceeds, gentle surgical technique is required, particularly at the fascial level, to avoid traction injuries to the small perforating vessels. Generally, the surgical technique is to skeletonize the vascular pedicle and keep the field dry.^{111,112}

Dozens of new perforator flaps have been described in the past decade. However, there is a core group of very useful perforator flaps which have become standard, including DIEAP flap,^{38,107,108} anterolateral thigh flap (based on the descending branch of the lateral circumflex femoral vessels through vastus lateralis, LCFAP-vl),¹¹³ submental artery flap (SMAP),¹¹⁴ posterior interosseous flap (PIOAP-s),¹¹⁵ thoracodorsal artery perforator flap (TAP-ld),¹¹⁶ superior gluteal artery (SGAP-gm),¹¹⁷ and inferior gluteal artery perforator flap (IGAP-gm).¹¹⁸ Depending on surgeon experience and preference, a number of these have replaced conventional flaps. The anterolateral thigh flap, in particular, has been called the ideal free flap, because of its usefulness in a wide variety of clinical applications.¹¹⁹ The perforator flaps are thoroughly described in a textbook on perforator flaps.³⁹ More recently, local perforator flaps have become increasingly utilized as a method of wound closure to provide tissues with good color match and contour and often avoid a free tissue transfer.^{120,121}

As Pribaz and Chan state, “The use of perforator flaps is a new and exciting paradigm in reconstructive surgery.”¹²²

The delay phenomenon

The only documented method to increase skin flap survival is the delay procedure. A delay procedure can be done in a variety of ways, from a partial incision around the margin of a planned flap, ligation of non-pedicle vessels supplying the flap, to partial or complete flap elevation (Fig. 21.53). The delay can be done in one or many stages and can lead to significantly improved skin flap survival. The physiologic effect of delay is an enlargement of the existing arteries along the axis of the flap, which has been well documented in experimental animal models (Figs. 21.54, 21.55).^{88,123,124} One adjacent anatomic vascular territory can be captured with safety on the cutaneous artery at the flap base. Anastomotic vascular keystones, usually formed by reduced-caliber choke arteries that link adjacent cutaneous perforators, play an integral role in the delay phenomenon. When a flap is elevated,

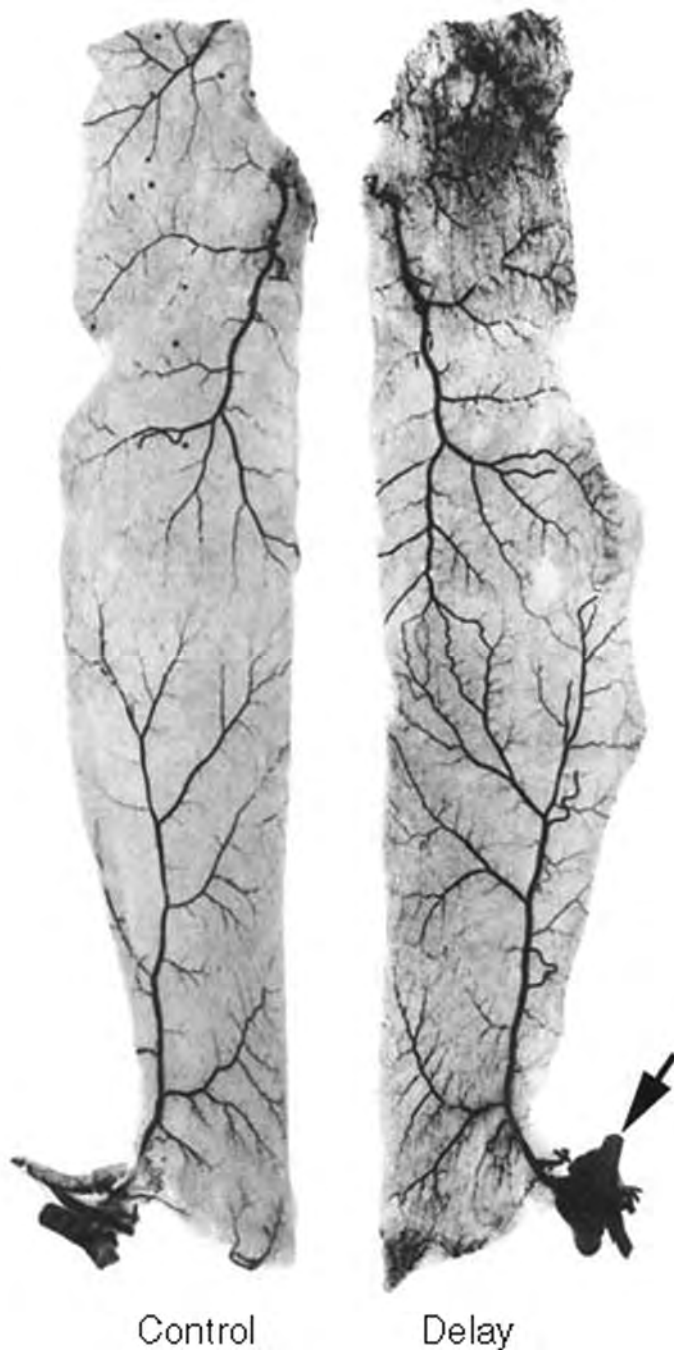


Fig. 21.55 Arteriogram of control (left) and delayed (right) rectus abdominis muscle of a dog 12 weeks after re-anastomosis of the previously ligated deep inferior epigastric artery (arrow). Note that the choke vessels remain tortuous and dilated, revealing that the effect of the delay is permanent and irreversible. (From Dhar SC, Taylor GI. *The delay phenomenon: the story unfolds*. *Plast Reconstr Surg*. 1999;104:2079.)

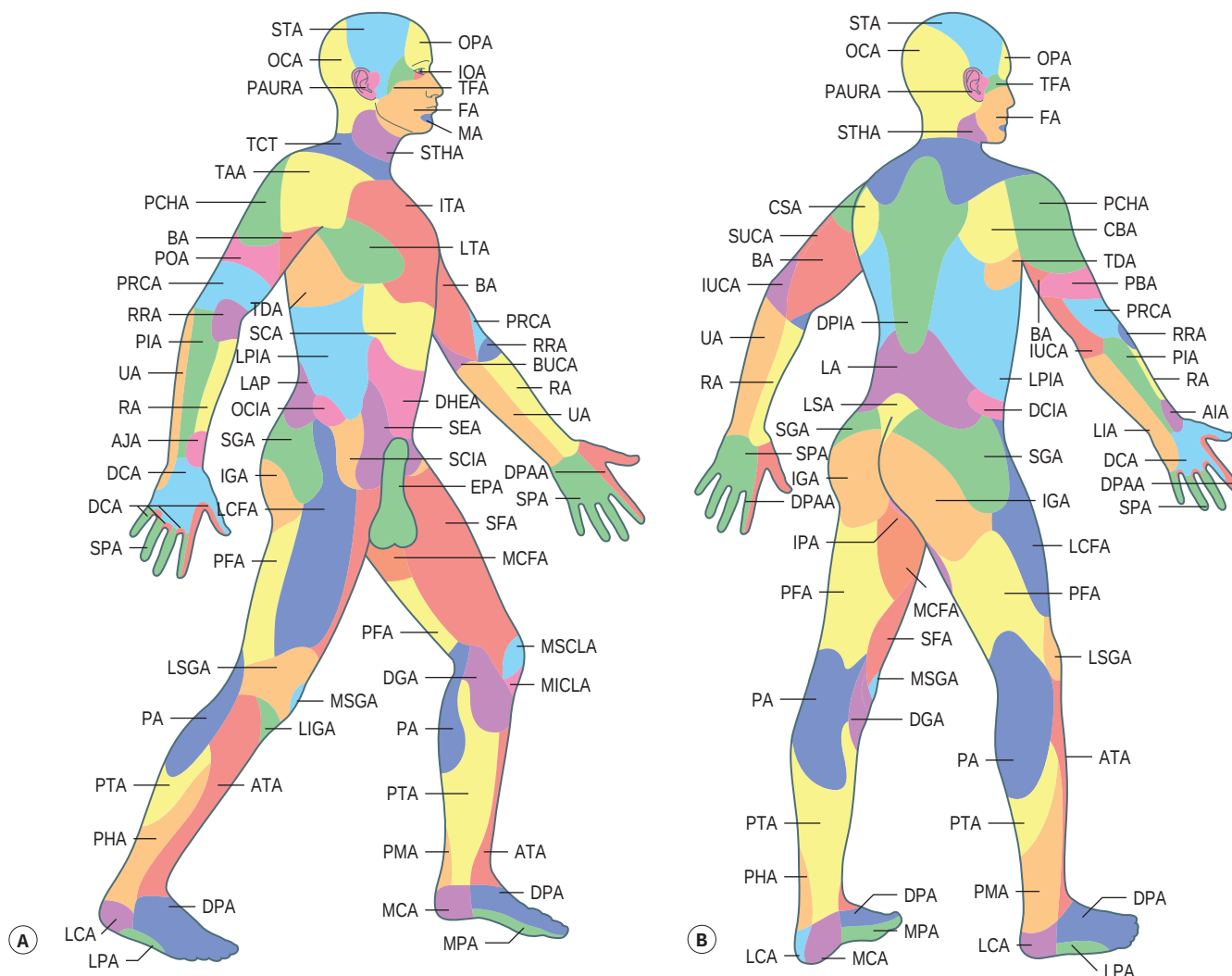


Fig. 21.51 Perforator vascular territories of the human body. The vascular territories of the body which correspond to regions of musculocutaneous and septocutaneous perforators to the skin. AIA, anterior interosseous artery; ATA, anterior tibial artery; BA, brachial artery; CSA, circumflex scapular artery; DCA, dorsal carpal arch; DCIA, deep, circumflex iliac artery; DGA, descending genicular artery; DIEA, deep inferior epigastric artery; DPA, dorsal pedis artery; DPAA, deep palmar arch; DPIA, dorsal branch of posterior intercostal artery; EPA, external pudendal artery; FA, facial artery; IGA, inferior gluteal artery; IOA, infraorbital artery; IPA, internal pudendal artery; ITA, internal thoracic (mammary) artery; IUCA, inferior ulnar collateral artery; LA, lumbar arteries; LCA, lateral calcaneal artery; LCFA, lateral circumflex femoral artery; LIGA, lateral inferior genicular artery; LPA, lateral plantar artery; LPIA, lateral branches of posterior intercostal artery; LSA, lateral sural artery; LSGA, lateral superior genicular artery; LTA, lateral thoracic (mammary) artery; MA, mental artery; MCA, medial calcaneal artery; MCFA, medial circumflex femoral artery; MIGA, medial inferior genicular artery; MSA, medial sural artery; MSGA, medial superior genicular artery; OCA, occipital artery; OPA, ophthalmic artery; PA, popliteal artery; PAURA, posterior auricular artery; PBA, profunda brachial artery; PCHA, posterior circumflex humeral artery; PFA, profunda femoris artery; PIA, posterior interosseous artery; PNA, peroneal artery; PRCA, posterior radial collateral artery; PTA, posterior tibial artery; RA, radial artery; RRA, radial recurrent artery; SCIA, superficial circumflex iliac artery; SEA, superior epigastric artery; SFA, superficial femoral artery; SGA, superior gluteal artery; SIEA, superficial inferior epigastric artery; SMA, submental artery; SPA, superficial palmar arch; STA, superficial temporal artery; STHA, superior thyroid artery; SUCA, superior ulnar collateral artery; TAA, thoracoacromial artery. (From Geddes CR. MSc thesis. Dalhousie University, Halifax, Nova Scotia, Canada.)

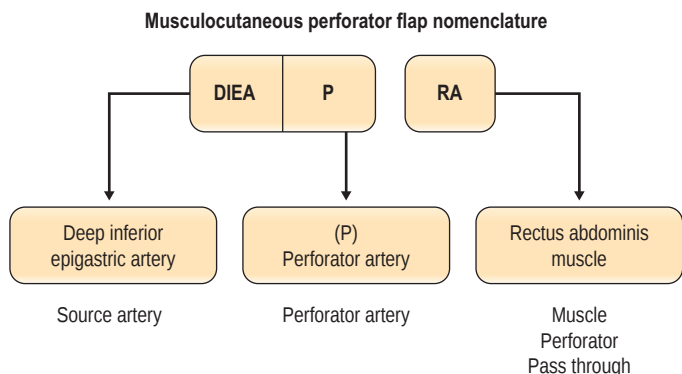


Fig. 21.52 Perforator flap nomenclature. (From Geddes CR, Morris SF, Neligan PC. Perforator flaps – evolution, classification and applications. *Ann Plast Surg*. 2003;50:90–99.)

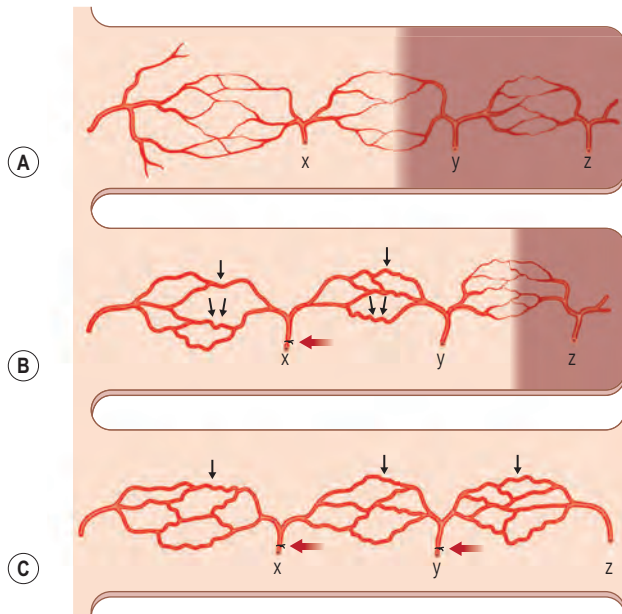


Fig. 21.53 Diagrammatic representation of the same flap raised with and without a surgical delay to illustrate the necrosis line and the changes in the choke vessels. **(A)** The adjacent territory x is captured with safety, and the necrosis line occurs at the choke–vessel interface with vessel y or the one beyond. **(B)** Vessel x had been delayed. Note the effect on the choke vessels and the site of the necrosis line. **(C)** Vessels x and y have been delayed in this bipedicle flap. Vessel z is divided and the tip of the flap elevated at a second stage to provide the longest flap. (From Callegari PR, Taylor GI, Caddy CM, et al. *An anatomic review of the delay phenomenon I: experimental studies*. *Plast Reconstr Surg*. 1992;89:397–418.)

these choke vessels, which initially reduce flow from one arterial territory to the next along the flap, enlarge to the caliber of the cutaneous arteries they connect. However, this process of vessel enlargement is an active event and takes time. It is a permanent and irreversible process involving multiplication and hypertrophy of the cells in each layer of the vessel wall, with its maximal effect occurring between 48 and 72 hours after operation (Fig. 21.56).¹²³ It has been observed that necrosis usually occurs at the level of the next choke anastomosis in the arterial network or the one beyond. Surgically, flap survival can be extended by the strategic division of vascular pedicles at various time intervals along the length of the proposed flap – the “flap delay” procedure.

Composite flaps

A knowledge of the vascular supply of all the tissues that constitute each angiosome provides the basis for the transfer

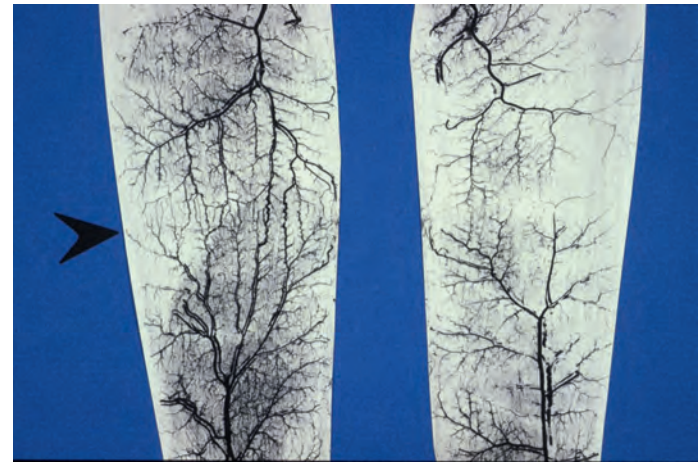


Fig. 21.54 Arteriogram of control (left) and delayed (right) rectus abdominis muscles of a dog 7 days postoperatively. Note the dilated choke vessels in the delayed flap by ligation of the deep inferior epigastric artery (arrow). (From Dhar SC, Taylor GI. *The delay phenomenon: the story unfolds*. *Plast Reconstr Surg*. 1999;104:2079.)

of composite units of skin, muscle, nerve, tendon, and bone supplied by a single arteriovenous system. This knowledge has been applied extensively in free composite tissue transfer. The vessels within the angiosome interconnect between the various layers. This interconnection is well illustrated with the transfer of composite tissue from the groin region. The direct cutaneous perforators of the superficial circumflex iliac artery interconnect with the indirect perforators of the deep circumflex iliac artery. When a composite osteocutaneous flap is based on the deep system, the perforators of the deep circumflex iliac artery capture the territory of the superficial circumflex iliac artery to perfuse the skin.⁶⁶ When the superficial system is used, the reverse applies to perfuse the anterior segment of iliac crest and the attached muscles.⁶⁸

Angiosome concept and flap design

In this chapter, we have presented a variety of anatomical information which supports the angiosome concept and which provides a blueprint for successful flap design. As always in the course of surgical evolution, the ideas and concepts will gradually change to reflect new discoveries and the pioneering efforts of creative surgeons. Surgical advances move as the pendulum in an undulating course, ever closer to the true course.



Bonus images for this chapter can be found online at

<http://www.expertconsult.com>

Fig. 21.3 Carl Manhot's vascular territories of the human integument. **(A)** Cutaneous vascular territories, ventral surface. **(B)** Cutaneous vascular territories, dorsal surface. (From Manhot C. *Die Hautarterien des menschlichen Körpers*. Leipzig: FCW Vogel, 1889.)

Fig. 21.4 Michel Salmon's vascular territories of the human integument, 1936. Summary of the cutaneous arterial territories of the ventral surface of the body. (From Salmon M. *Artères de la peau*. Paris: Masson, 1936.)

Fig. 21.5 Cadaver with body landmarks and incision lines marked. (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113.)

Fig. 21.6 Lateral view of one female subject **(A)** and anterior view of another **(B)**. **(A)** The arm has been removed. Note the network of large vessels that sweep laterally from the ventral and dorsal midlines, ascend from the groins, descend from the shoulder girdle, and converge on the summits of the scalp and the breasts. This demonstrates the principle that vessels radiate from fixed concave zones and radiate to mobile convex areas. **(B)** A lower midline scar interrupts the vessels with compensatory opening of a large choke vessel above the umbilicus (arrow) to re-establish the flow across the midline. (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113.)

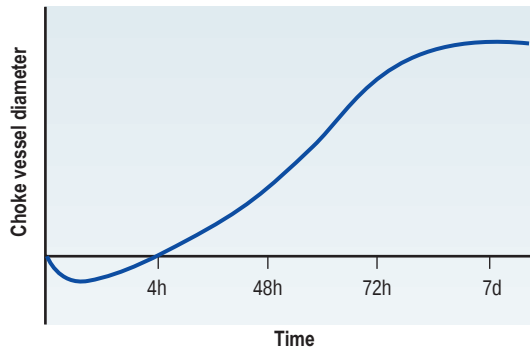


Fig. 21.56 Time sequence of delay. Immediately after the surgical elevation of a flap, the overall vascular diameter is reduced by vasoconstriction. Following this, gradual dilation occurs during the first 48 hours, and then dramatic dilation occurs from 48 to 72 hours. The rate of vessel enlargement then begins to plateau, and gradually, vessels increase thereafter.

Fig. 21.16 Arterial injection of the right upper limb and torso. **(A)** Note the chain-linked systems of arteries (arrows) that course with the cutaneous nerves in the upper limb. **(B)** On the torso, the nerves are marked on the arterial study. They course with the cutaneous arteries, cross them at angles and collect arterial branches, or approach the arteries from opposite directions (arrows). (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg.* 1987;40:113; and Taylor GI, Gianoutsos MP, Morris SF. The neurovascular territories of the skin and muscles: anatomic study and clinical implications. *Plast Reconstr Surg.* 1994;94:1.)

Fig. 21.19 **(A)** Arteriogram of the skin of the pig. Note numerous small perforators on lateral torso, a superficial vein that has filled in the study (arrow), the larger segmental vessels near the ventral and dorsal midline, and the large perforator of the deep circumflex iliac artery near the hip. **(B)** Angiogram of the dog. Note the large perforator of the deep circumflex iliac artery and the thoracodorsal artery (arrows) near the hip and shoulder, respectively. **(C)** Arteriogram of the rabbit. Note the very large perforators of the deep circumflex iliac artery and thoracodorsal arteries dorsally and the superficial inferior epigastric artery and lateral thoracic arteries ventrally. Note also the large vessels supplying the ear. **(D)** Arteriogram of the duck. Note the discrete territories bounded by choke arteries and the long, stretched-out perforator of the transverse cervical artery in the mobile skin area of the neck (arrow). (From Taylor GI, Minabe T. The angiosomes of the mammals and other vertebrates. *Plast Reconstr Surg.* 1992;89:181.)

Fig. 21.20 Injection studies of the anterior torso with the integument removed and umbilicus located (large dot). The studies of the human and dog **(A and C)** are almost identical, with the deep inferior epigastric artery larger than the deep superior epigastric artery. In the pig and rabbit **(B and D)**, the reverse applies. (From Taylor GI, Minabe T. The angiosomes of the mammals and other vertebrates. *Plast Reconstr Surg.* 1992;89:181.)

Fig. 21.21 Comparative study of the rectus abdominis muscle from the various mammals studied. There is a striking similarity between the studies. However, in all animals except the pig, the muscle extends on to the thorax more cranially than in the human, and this region of the rectus receives additional branches from the internal thoracic artery. The reciprocal size relationship of the deep superior epigastric artery and deep inferior epigastric artery between species is a good example of the law of equilibrium. (From Taylor GI, Minabe T. The angiosomes of the mammals and other vertebrates. *Plast Reconstr Surg.* 1992;89:181.)

Fig. 21.26 The cutaneous perforators of the forearm, color-coded to match the angiosomes. Large and small skin perforators are indicated by size of the colored markers. Compare with **Fig. 21.22**. (From Inoue Y, Taylor GI. The angiosomes of the forearm: anatomic study and clinical applications. *Plast Reconstr Surg.* 1996;98:195.)

Fig. 21.27 The vascular territories of the **(A)** superficial, **(B)** middle, and **(C)** deep forearm flexor muscles. Note that the junctional zone between angiosomes occurs primarily within the muscles and that most muscles cross at least two angiosomes. Compare with **Figs. 21.23** and **21.24**. (From Inoue Y, Taylor GI. The angiosomes of the forearm: anatomic study and clinical applications. *Plast Reconstr Surg.* 1996;98:195.)

Fig. 21.28 The vascular territories of the **(A)** superficial and **(B)** deep forearm extensor muscles, showing once again that the junctional zone lies primarily within the muscles. (From Inoue Y, Taylor GI. The angiosomes of the forearm: anatomic study and clinical applications. *Plast Reconstr Surg.* 1996;98:195.)

Fig. 21.29 Cross-sectional studies of the forearm at the level of **(A)** the head of the radius, **(B)** insertion of the pronator teres, and **(C)** midforearm, showing the angiosomes of the forearm: brachial (yellow), radial (blue), ulnar (red), anterior interosseus (green), and posterior interosseous (orange) arteries. Note that the junctions of the angiosomes occur within the skin, within the muscles, and within the bone. (From Inoue Y, Taylor GI. The angiosomes of the forearm: anatomic study and clinical applications. *Plast Reconstr Surg.* 1996;98:195.)

Fig. 21.30 Vascular territories of the lower leg. The colored circles represent cutaneous perforators emerging from the deep fascia and depict relative size of the vessels. (From Taylor GI, Pan WR. The angiosomes of the leg: anatomic study and clinical applications. *Plast Reconstr Surg.* 1998;102:599.)

Fig. 21.31 Vascular territories of the lower leg. **(A)** Illustration of the anterior muscle group that lies totally within the anterior tibial angiosome (blue). This angiosome extends to include part of the peroneal muscles. **(B)** Illustration of the lateral muscles and their supply from the anterior tibial (blue) and peroneal (green) angiosomes. (From Taylor GI, Pan WR. The angiosomes of the leg: anatomic study and clinical applications. *Plast Reconstr Surg.* 1998;102:599.)

Fig. 21.32 Vascular territories of the lower leg. **(A)** The superficial muscle group with its supply from the arteries of the popliteal (purple), sural (orange), posterior

tibial (yellow), and peroneal (green) angiosomes. All muscles cross at least two angiosomes and receive branches from the source arteries of each. **(B)** The deep muscles and their supply form the source arteries of each angiosome. (From Taylor GI, Pan WR. The angiosomes of the leg: anatomic study and clinical applications. *Plast Reconstr Surg.* 1998;102:599.)

Fig. 21.33 **(A–C)** Vascular territories of the lower leg. Anterior view of the leg with cross-sections at three levels, viewed distally. The figures show angiosomes of the anterior tibial (blue), posterior tibial (yellow), peroneal (green), and sural (orange) arteries. Note in each case that the angiosome territories extend from the skin to the bone and that their borders, defined by anastomotic vessels, meet usually within tissues, especially the muscles, rather than between them. (From Taylor GI, Pan WR. The angiosomes of the leg: anatomic study and clinical applications. *Plast Reconstr Surg.* 1998;102:599.)

Fig. 21.34 Fresh cadaver lead oxide arterial study of the lateral **(A)** and anterior **(B)** view of the composite skin and superficial musculoaponeurotic system (SMAS) unit in the head and neck. The occipital (a), superficial temporal (b), and ophthalmic (c) arteries have been labeled. Note that the facial vein (v) runs a more direct course and at some distance to its arterial counterpart, the facial artery (d). **(C)** The skin layer alone reveals a vast arterial “blush” zone of the skin and SMAS shown in sagittal view. Note: (1) the rich arterial anastomotic “waves” formed between the branches of the occipital, superficial temporal, and ophthalmic arteries in the scalp; (2) the cluster of small vessels supplying the fixed skin area over the parotid gland and masseter muscle compared with the large branches of the facial artery that supply the mobile anterior face; and (3) the relative paucity of large vessels in the neck except in the anterior triangle. The SMAS layer is seen only in **(D)** with the muscles of facial expression outlined. (From Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. *Plast Reconstr Surg.* 2000;105:2287.)

Fig. 21.35 **(A)** Lead oxide arterial study of the blood supply of the ear and adjacent tissues. Note the arcades formed between the superficial temporal and posterior auricular arteries, highlighted with arrows. **(B)** Schematic picture shows the branches of the superficial temporal (dark) and posterior auricular (light) supply to the front and back of the ear, respectively. Note also the true and choke anastomoses between these two arteries in the scalp. **(C, D)** Close-up examination of the arterial anatomy of the external nose. Note the arcades that occur around the alar dome between the columella branch of the superior labial artery and the facial artery. The facial vein has also been partially filled with lead oxide and highlighted by the arrows. (From Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. *Plast Reconstr Surg.* 2000;105:2287.)

Fig. 21.36 Angiosomes of the muscles of facial expression and mastication in the face. (From Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. *Plast Reconstr Surg.* 2000;105:2287.)

Fig. 21.37 **(A–D)** The angiosomes of the head and neck colored and numbered to match **Figs. 21.22** and **21.35**. (From Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. *Plast Reconstr Surg.* 2000;105:2287.)

Fig. 21.38 Radiograph of the tongue; note the almost avascular midline. (From Houseman ND, Taylor GI, Pan WR. The angiosomes of the head and neck: anatomic study and clinical applications. *Plast Reconstr Surg.* 2000;105:2287.)

Fig. 21.39 Diagram showing how the size and course of the direct cutaneous perforators x and y, which emerge from fixed points in the deep fascia, could be modified by growth either before or after birth. **(A)** The perforators, which are fixed in number and position, form a major connecting network on the surface of the deep fascia in the “resting state”. **(B)** They are stretched with the deep fascia by the expansion of underlying tissues (e.g., the scalp vessels as the brain and skull expand during fetal development). **(C)** As the breast develops within the integument, the vessels are displaced toward the dermis and lengthened as they converge on the nipple. **(D)** They are stretched apart in the limbs as the long bones grow, but they still retain their original relationship to the deep fascia. **(E)** The vessels are again stretched apart by growth, but the mobile relationship between the undersurface of the integument and the deep fascia is responsible for their oblique course. This pattern is characteristic of the loose skin areas of the torso. (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg.* 1987;40:113.)

Fig. 21.40 Dotted line through choke connecting vessels of a large acromioclavicular perforator to define its anatomic territory. Compare with **Fig. 21.16**, left side of chest. (From Taylor GI, Palmer JH. The vascular territories

[angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113.)

Fig. 21.41 Radiographs of the integument of the upper limb and hand. (A) The skin has been incised along the ulnar border. It has been removed (B) with the deep fascia and (C) without it. (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113.)

Fig. 21.42 The interconnecting arcades of the small intestine. (From Crosthwaite GL, Taylor GI, Palmer JH. A new radio-opaque injection technique for tissue preservation. *Br J Plast Surg*. 1987;40:497.)

Fig. 21.43 (A) The wing of a moth and (B) the leaf of a tree, showing their interconnecting arcades of "veins". (From Taylor GI, Palmer JH. The vascular territories [angiosomes] of the body: experimental study and clinical applications. *Br J Plast Surg*. 1987;40:113.)

Fig. 21.47 Doppler probe for the design of skin flaps. The handheld Doppler can be used to identify cutaneous perforators for the design of skin flaps. In this

case, the Doppler is used to design a flap based on perforators of the deep inferior epigastric vessels.

Fig. 21.55 Arteriogram of control (left) and delayed (right) rectus abdominis muscle of a dog 12 weeks after re-anastomosis of the previously ligated deep inferior epigastric artery (arrow). Note that the choke vessels remain tortuous and dilated, revealing that the effect of the delay is permanent and irreversible. (From Dhar SC, Taylor GI. The delay phenomenon: the story unfolds. *Plast Reconstr Surg*. 1999;104:2079.)

Fig. 21.56 Time sequence of delay. Immediately after the surgical elevation of a flap, the overall vascular diameter is reduced by vasoconstriction. Following this, gradual dilation occurs during the first 48 hours, and then dramatic dilation occurs from 48 to 72 hours. The rate of vessel enlargement then begins to plateau, and gradually, vessels increase thereafter.



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Flap classification and applications

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SYNOPSIS

- Flap is tissue(s) with its own vascular supply, allowing transfer from one site to another.
- Flaps come in various forms, shapes and function. They may be composed of a simple skin tissue or multiple composite tissues.
- The purpose of classification is to understand the anatomy and the features that each flap provides. It also allows communication not only with peers but with the patients as well to achieve the common goal of reconstruction.
- Various methods can be used to classify flaps, but commonly used classifications are based on the locality of the flap, vascular supply of the flap, and tissue components of the flap.
- By applying a precise knowledge of the anatomy of skin, muscle, bone, fascia, and other tissue in planning reconstructive procedures, the surgeon has the ability to restore function in congenital and acquired defects.
- This chapter reviews flap classification and gives examples of its applications.

History

The use of flaps for reconstructive plastic surgery dates back to 600 BC, when the earliest recorded application of pedicled flaps for nasal reconstruction is attributed to Sushruta Samhita (translated by Bhishagratna in 1916).¹ The earliest flaps centered on the head and neck as well as the lower extremities because wounds in these regions failed to heal by secondary intention. The initial flaps used would now be considered random-pattern flaps, as they were not based on a specific blood supply and were used without an understanding of how and why they survived. All possible flaps were based on the simple idea of random flaps.² Tagliacozzi used a distally-based arm flap in a two-staged procedure.³ His work was published in Venice in 1597. Much of this knowledge was forgotten until the 19th century, when the English surgeon Carpie successfully used forehead flaps to reconstruct the

noses of two officers.⁴ The publication of *Rhinoplastik* by von Graefe in 1818 further advanced the use of these techniques.⁵ Attention in the early 20th century remained focused on tubed random flaps. It was found that the only way to increase survival of these flaps was to perform a surgical delay. A German anatomist, Carl Manchot, demonstrated the concept of anatomic skin territories supplied by consistent vessels in *Die Hautarterien des Menschlichen Körpers*, published in 1889.⁶ Further development into the shape of modern flaps came with Tansini when he described the skin island of the latissimus dorsi musculocutaneous flap in 1906.⁷ Davis, crediting Manchot, demonstrated axial and pedicled muscle and fascial flaps, as well as composite flaps in 1919.⁸ McGregor introduced the temporalis flap, which allowed midface and lower face coverage without the donor site deformity associated with the previously popular forehead flap.⁹ Coverage of the lower third of the face as well as of the oral and esophageal defects was accomplished by Bakamjian with the use of the deltopectoral flap.¹⁰ The availability of the forehead, temporalis, and deltopectoral flaps changed the approach to head and neck cancer extirpative surgery with an emphasis on immediate reconstruction. A slow evolution of flaps was based on experience and gradual understanding of anatomy.

The muscle flap for lower extremity reconstruction was initially described by Stark for coverage of debridement sites for osteomyelitis.¹¹ Unfortunately, this went unnoticed until Ger recognized that the leg muscles are a source of well-vascularized tissue for leg coverage.¹² Although Owens, in 1955, used a compound flap consisting of the sternocleidomastoid muscle with overlying skin for head and neck reconstruction, the concept of musculocutaneous perforating vessels providing a cutaneous territory for superficial muscles was first reported by Orticochea in 1972.¹³ Shortly thereafter, surgeons made significant contributions toward definition of flaps, expansion, and use of muscle and musculocutaneous flaps in reconstructive surgery. The contributions included the concept of cutaneous territory of superficial muscles;¹⁴ anatomy of the muscles including specific arcs of rotation;^{15,16} applications of muscle and musculocutaneous flaps for breast,

Table 22.1 Timeline of the development of flap surgery

600 BC	Sushruta Samhita ¹	Pedicle flaps in the face and forehead for nasal reconstruction
1597	Tagliacozzi ³	Nasal reconstruction by tubed pedicle flap from arm; described "delay" of pedicle flap
1896	Tansini ²⁰⁷	Latissimus dorsi musculocutaneous flap for breast reconstruction (post-mastectomy)
1920	Gillies ³⁹⁷	Tubed pedicle flap
1946	Stark ¹¹	Muscle flaps for osteomyelitis
1955	Owens ¹⁹⁰	Compound neck flap
1963	McGregor ⁹	Temporalis flap
1965	Bakamjian ³⁹⁸	Deltpectoral flap
1971	Ger ¹²	Lower extremity musculocutaneous flap
1972	McGregor and Jackson ³⁹⁹	Groin flap
1972	Orticochea ³⁶⁹	Musculocutaneous flaps
1977	McCraw <i>et al.</i> ¹⁴	Musculocutaneous territories
1981	Mathes and Nahai ¹⁶	Classification of muscle flaps based on vascular anatomy
1981	Ponten ²³	Fasciocutaneous flaps

chest, extremity, and head and neck reconstruction; and microsurgical transplantation.^{17–22} In 1981, Ponten recognized the input of septocutaneous perforating vessels to the overlying skin circulation.²³ On the basis of this observation, the concept of fasciocutaneous flaps was introduced. Like the muscle flap, the septocutaneous flap was initially described in the lower extremity, but the principle of the fasciocutaneous flap, based on muscle, fascia, and associated cutaneous territories, was rapidly applied to all body regions (Table 22.1).

Starting in the late 1970s, a proliferation of innovative techniques reported in the surgical literature throughout the world defined new anatomic data and applications of the muscle, musculocutaneous, fascial, and fasciocutaneous flaps. These advances in flap definition and application have changed the entire approach to plastic surgery. With the isolation of the vascular pedicles to muscle- and fascia-based flaps, microsurgical transplantation is selected when the ideal flap is outside of a traditional and safe arc of rotation to the recipient site. With the definition of musculocutaneous and fasciocutaneous territories, an expander may be used to enlarge flap dimensions and still ensure direct closure of the donor site. The reconstructive ladder, introduced in 1982, was appropriate for use in choosing reconstructive methods that ensure safety in soft-tissue reconstruction.²⁴ With increased understanding of the flap anatomy, physiology and even in regards to donor morbidity, ideal form and function can be achieved by complex procedures without compromising safety. This new approach can be considered as an elevator approach to defects entailing most of the issues to achieve a minimal

staged and ideally functional reconstruction.²⁵ Furthermore, donor site deformity is frequently avoided because the flap can be precisely tailored to fit the defect. In 1997, the reconstructive triangle was introduced to guide the thinking of complex reconstruction.²⁶ The surgeon may choose the transposition flap, microsurgical transplantation, or tissue expansion with the goals of achieving form and function at the recipient site, avoiding donor site deformity, and providing safety throughout the reconstructive endeavor. The more recent introduction of perforator flaps has expanded our options even more and brought us to the era of free-style flaps.²⁷ With all the explosive introduction of new flaps, new ideas and new findings, a classification may not describe all the innovations involved in the field of reconstruction. Furthermore, the introduction of the corresponding ideas and nomenclature increases the confusion.

This chapter describes the flap classification based on the important characteristics of the flap. The atomic classification of Tolhurst naturally involved the early flap characteristics and further refinements from Lamberty and Healy describe the most important factors for flap selection; circulation, constituents, conformation, contiguity, construction, and condition.^{28,29} Further modifications have been made to accommodate the recent introduction of flaps. In addition, application of these flaps will be introduced in this chapter.

Classification of flaps

A flap consists of tissue that is mobilized on the basis of its vascular anatomy. Flaps can be composed of skin (including subcutaneous fat), skin and fascia, skin and muscle, or skin, muscle and bone, or various compositions of tissues. Because the circulation to the tissue to be mobilized is crucial for flap survival, the development of flap techniques has depended on defining the vascular anatomy of the skin and underlying soft tissue.

The first classification can be made for a random pattern flap with a non-identified pedicle versus flaps with an identified pedicle. An early concept of vascular anatomy as it pertained to flap surgery was the belief that skin circulation was based on the longitudinal subdermal plexus. A random pattern flap based on this subdermal plexus was designed to allow elevation of skin and subcutaneous tissue with a certain length:width ratio in the range of 2–1.5:1. Based on the simplicity of circulation, the shape and movement of the flap were important distinguishing factors (Fig. 22.1). Milton subsequently disproved the concept of length-to-width ratios as viability depended on the extent of circulation.³⁰ He further proved his concept by showing that a delay procedure on the flap can further increase the extent of the flap in a pig model.³¹ Historically, attempts to use a random pattern flap based on subdermal circulation distant from the wound location eventually resulted in the introduction of the tubed pedicle flap. Through a series of delays using the initial bipedicle flap design, the arc of rotation of the skin flap was increased. Alternatively, the flap was attached to an arm carrier, which later required transferring the arm carrier of the random pattern flap from one body region (donor site) to another (recipient site). This use of the random pattern flap with multiple delays or the arm carrier allowed reconstruction of distant complex defects, particularly in the head and neck

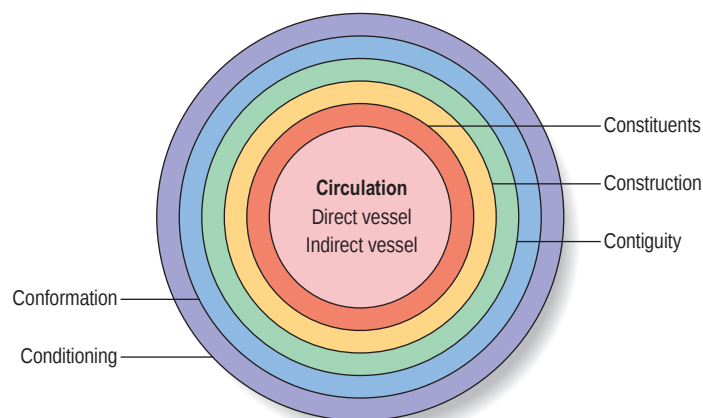


Fig. 22.3 Updated modified “atomic system” with “six Cs” of flap characteristics, but especially “core” or source of flap circulation, where each has a distinct role in determining flap nomenclature. (From Hallock GG. *The complete classification of flaps*. Microsurgery. 2004;24:157–161.)

toward the defect with minimal tension. Because of the large size of the flap, identification of the vascular source is not necessary and it is presumed to have various blood supplies from the perforators entering from the deep fascia. But when perforators are identified using a Doppler, one can also call this a keystone-design perforator island flap.³²

Previously with random pattern flaps, type of movement, shape of the flap or anatomical region was the focus for differentiating the types. But as the anatomy of the vessel became more evident and the importance recognized, flap description began to depict the circulation.²⁸ The evolution from random pattern flaps to fasciocutaneous flaps, myocutaneous flaps and then recently to perforator flaps was based on the development and findings of vascular anatomy throughout the body. Pioneering work from Manchot, Salmon, Cormack, Lamberty, Taylor, Morris, Tang, Nakajima and others clarified the vascular anatomy for skin territory originating from a source vessel.^{6,29,33–37} The flap elevation practice changed with the work of Taylor and Palmer presenting the angiosome concept, which increased our knowledge of vascular territory of the skin flap.³³ Now the concept of vascular territory has evolved from thinking of the angiosome as the basic unit to applying the perforator as the basic unit, termed “perforasome”.³⁸

Circulation being clearly the most important characteristic of flaps with identified pedicle, Cormack and Lamberty were the first to advocate the source of the circulation as the most important characteristic of flap selection.²⁹ The six Cs included, in addition to circulation, constituents (composition), conformation (form/shape), contiguity (destination), construction (type of pedicle), and conditioning (preparation) (Fig. 22.3). Hallock further outlined this classification in accordance with the six Cs and named it “complete classification of flaps”.³⁹ With the addition of recent flaps and advances, a modified outline for the basis of flap classification is shown in Table 22.2.

This approach to muscle flaps can be demonstrated with the gracilis muscle flap shown in Fig. 22.4:

- Circulation: medial circumflex femoral artery
- Constituents: gracilis muscle
- Contiguity: free flap
- Construction: antegrade flow

Table 22.2 The basis for flap classification

1. Circulation (blood supply)

Direct vessels
axial
septocutaneous
endosteal
Indirect vessels
myocutaneous
periosteal

2. Constituents (composition)

Skin (with subcutaneous fat)
Fasciocutaneous/fascia
Muscle/musculocutaneous
Visceral
Nerve
Bone
Cartilage
Lymph node (with subcutaneous fat)
Other

3. Contiguity (destination)

Local
Regional
Distant (free)

4. Construction (flow)

Unipedicle*
Bipedicle
Antegrade*
Retrograde (reverse)
Turbocharged
Supercharged
Arterialized venous

5. Conditioning

Delay
Tissue expansion
Prefabrication
Sensate (sensory nerve)
Functional (motor nerve)
None*

6. Conformation

Special shapes
Tubed
Combined flaps
None*

*Denotes default or standard for flaps and can be omitted in the use of complete classification.

- Conditioning: none
- Conformation: muscle only

Thus the gracilis muscle flap from Fig. 22.4 can be named medial circumflex femoral artery-based (circulation) gracilis muscle (constituents) free (contiguity) flap with antegrade flow (construction) with no conditioning (conditioning) and muscle only (conformation) according to the complete classification. But, as default, “antegrade flow with no conditioning” can be omitted from the nomenclature. Also, since there is one conformation, “muscle” does not have to be repeated and, finally, since the circulation from the “medial circumflex

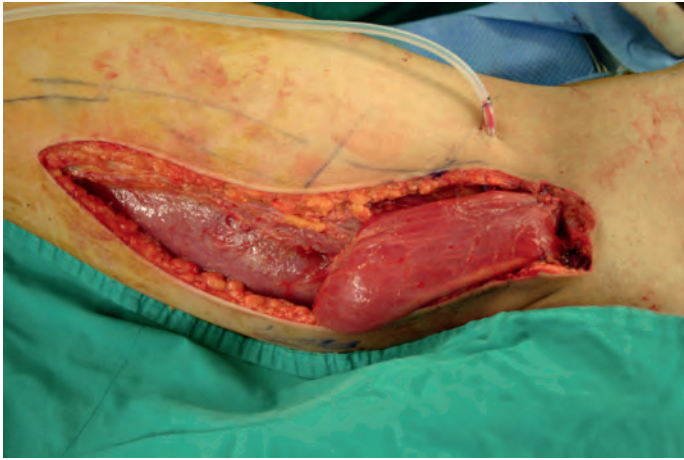


Fig. 22.4 Example of a gracilis muscle flap. It can be named a medial circumflex femoral artery-based (circulation) gracilis muscle (constituents) free (contiguity) flap with antegrade flow (construction) with no conditioning (conditioning) and muscle only (conformation) according to the complete classification.

femoral artery” is an established one for any muscle flaps, this can be considered to be understood and does not have to be reiterated. Thus the final classification using the “complete classification” can be described as “gracilis muscle free flap”.

For muscle flaps, the circulation can be from multiple variations and these variations play an important part in survival of each muscle flap. Therefore further classification of muscle flaps should be addressed.¹⁶

The next example would be a musculo-fascio-cutaneous flap from the same region as shown in Fig. 22.5:

- Circulation: medial circumflex femoral artery
- Constituents: gracilis muscle and upper medial thigh fasciocutaneous
- Contiguity: free flap

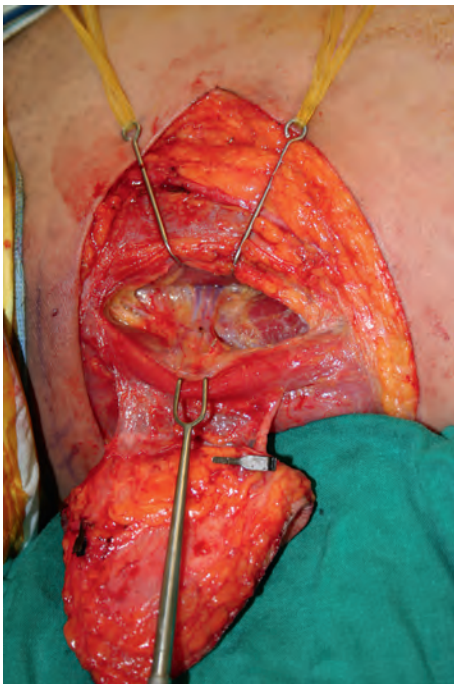


Fig. 22.5 Example of a musculo-fascio-cutaneous flap including the gracilis muscle and the combined skin and fascia.

- Construction: antegrade flow
- Conditioning: none
- Conformation: combined muscle and fasciocutaneous flap

The flap in Fig. 22.5 can be named as medial circumflex femoral artery-based (circulation) gracilis muscle (constituents) free (contiguity) flap with antegrade flow (construction) with no conditioning (conditioning) and combined with muscle and fasciocutaneous component (conformation) according to the complete classification. As defaults are omitted from the nomenclature, the “complete classification” should be: “combined gracilis musculo(-fascio-)cutaneous free flap”.

The actual source of circulation feeding the subdermal plexus of the skin was described in a tripartite system from Cormack and Lamberty.²⁹ The system consisted of axial (direct cutaneous), musculocutaneous, and fasciocutaneous types of free flaps. They further described the fasciocutaneous flap into subtypes leading to the fasciocutaneous flap classification.⁴⁰ These classifications should be recognized as they rely on the anatomical vascular system of the flap and improve the design and survival of the flaps.

When the skin portion of this flap is isolated on a single perforator, the constituents become a combination of medial circumflex artery perforator flap and gracilis muscle flap. Combined flaps with identified circulation can also undergo a classification for combined/compound flaps.^{41,42} Thus, this variation of flap should be named “combined (conjoint) medial circumflex femoral perforator and gracilis muscle free flap”.

The final example is shown in Fig. 22.6. Note that this flap from the upper medial thigh is supplied only with a perforator.

- Circulation: medial circumflex femoral artery (perforator)
- Constituents: upper medial thigh skin (with fat)

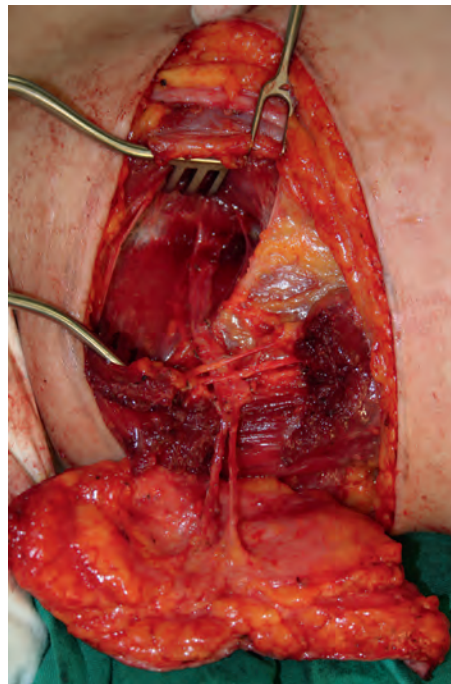


Fig. 22.6 Example of flap from the upper medial thigh, supplied only with a perforator without the gracilis muscle and the fascia.

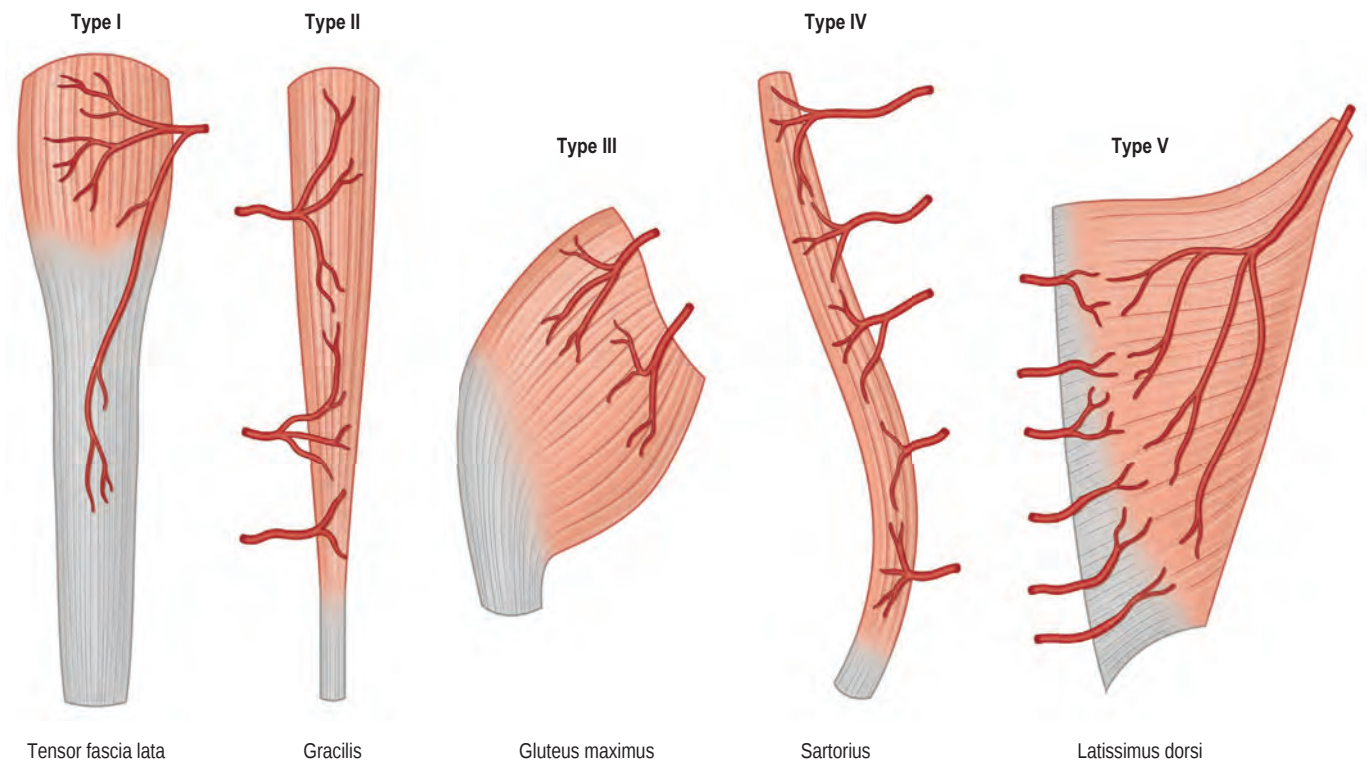


Fig. 22.7 Mathes–Nahai classification of muscle and musculocutaneous flaps.

- Contiguity: free flap
- Construction: antegrade flow
- Conditioning: none
- Conformation: skin (with fat) only

The circulation to this flap is the same source vessel as the gracilis muscle or musculocutaneous flap. But this is a flap supplied with an identified perforator, so recognition should be made of the perforator as the main circulation. Thus, this flap should be named as “medial circumflex femoral artery perforator-based (circulation) upper medial thigh skin (with fat) (constituents) free (contiguity) flap with antegrade flow (construction) with no conditioning (conditioning) and skin only component (conformation) according to the complete classification. As defaults are omitted from the nomenclature, the “complete classification” should be “medial circumflex femoral artery perforator skin flap”.

This type of perforator-based flap has been subject to controversy as there have been many classifications proposed. The Gent consensus for classification of perforator flaps will be reviewed as an example of perforator flap classification.

Flaps based on the constituents

Muscle and musculocutaneous flaps

In 1981, Mathes and Nahai described a classification system for muscles based on the following anatomic relationships between the muscle and its vascular pedicles:

1. The regional source of the pedicle entering the muscle
2. The number and size of the pedicle
3. The location of the pedicle with respect to the muscle’s origin and insertion

4. The angiographic patterns of the intramuscular vessels.

This classification system enables the surgeon to categorize the various muscle and musculocutaneous flaps into distinctly different, clinically applicable groups based on the vascular anatomy. There are five different vascular patterns by which the various muscles are categorized (Fig. 22.7).¹⁶

Type I: one vascular pedicle – Type I muscles are supplied by a single vascular pedicle (Table 22.3).

Type II: dominant vascular pedicle and minor pedicle – Type II muscles are supplied by both a dominant and minor vascular pedicle. The larger dominant vascular pedicle will usually sustain circulation to these muscles after the elevation

Table 22.3 Type I vascular pattern muscles
Abductor digiti minimi (hand)
Abductor pollicis brevis
Anconeus
Colon
Deep circumflex iliac artery
First dorsal interosseous
Gastrocnemius, medial and lateral
Genioglossus
Hyoglossus
Jejunum
Longitudinalis linguae
Styloglossus
Tensor fascia lata
Transversus and verticalis linguae
Vastus lateralis

of the flap when the minor pedicles are divided. This is the most common pattern of circulation observed in human muscle (Table 22.4).

Type III: two dominant pedicles – Type III muscles possess two large vascular pedicles from separate vascular sources. These pedicles have either a separate regional source of circulation or are located on opposite sides of the muscle. Division of one pedicle during flap elevation rarely results in loss of muscle within its vascular distribution. The muscle will usually survive on one of its two dominant vascular pedicles.

Table 22.4 Type II vascular pattern muscles

Abductor digiti minimi (foot)
Abductor hallucis
Brachioradialis
Coracobrachialis
Flexor carpi ulnaris
Flexor digitorum brevis
Gracilis
Hamstring (biceps femoris)
Peroneus brevis
Peroneus longus
Platysma
Rectus femoris
Soleus
Sternocleidomastoid
Trapezius
Triceps
Vastus medialis

Table 22.5 Type III vascular pattern muscles

Gluteus maximus
Intercostal
Omentum
Orbicularis oris
Pectoralis minor
Rectus abdominis
Serratus anterior
Temporalis

Table 22.6 Type IV vascular pattern muscles

Extensor digitorum longus
Extensor hallucis longus
External oblique
Flexor digitorum longus
Flexor hallucis longus
Sartorius
Tibialis anterior

Table 22.7 Type V vascular pattern muscles

Fibula
Internal oblique
Latissimus dorsi
Pectoralis major

This vascular pattern allows the muscle to be split, allowing the use of only part of the muscle as a muscle or musculocutaneous flap (Table 22.5).

Type IV: segmental vascular pedicles – Type IV muscles are supplied by segmental vascular pedicles entering along the course of the muscle belly. Each pedicle provides circulation to a segment of the muscle. Division of more than two or three of the pedicles during elevation as a flap may result in distal muscle necrosis (Table 22.6).

Type V: one dominant vascular pedicle and secondary segmental vascular pedicles – Type V muscles are supplied by a single dominant pedicle and secondary segmental vascular pedicles. These muscles have one large dominant vascular pedicle near the insertion of the muscle with several segmental pedicles near the origin. The internal vasculature can be supplied by either the dominant or the segmental pedicles, and therefore the muscle may be elevated as a flap on either vascular system (Table 22.7).

When a flap is used based on the pedicle as a local or an island flap, the dominant vascular pedicle to the flap is preserved. A factor that may prevent successful flap transposition is the flap's arc of rotation. The arc of rotation of a muscle is determined by the extent of elevation of the muscle from its anatomic bed and the ability of the muscle to reach adjacent areas without devascularization. The mobility of a muscle depends on the number of vascular pedicles and the location of the dominant vascular pedicle relative to the muscle's origin and insertion (Fig. 22.8). The area covered by the arc of rotation varies among individuals. On the basis of the flap

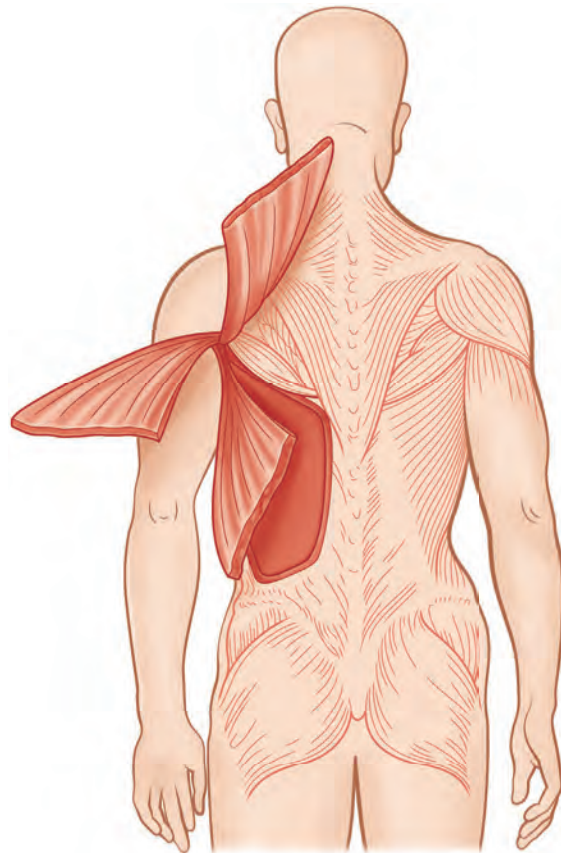


Fig. 22.8 Arc of muscle rotation (latissimus muscle).

length distal to the point of rotation and the length of the vascular pedicle, a safe standard arc of rotation is measured for each flap. A modified arc of rotation is also available based on refinements in design and specific modifications of the flap. Precise knowledge of the safe standard and modified arc of rotation is necessary to avoid loss of the flap from excessive tension or damage to the pedicle from overzealous dissection.

In general, the arc of rotation is inversely proportional to the number of vascular pedicles. If a muscle has a large number of pedicles, it usually has a limited arc of rotation. Type IV muscles, such as the sartorius and tibialis anterior, are examples of muscles with multiple segmental vascular pedicles and limited arcs of rotation. Similarly, the location of the dominant vascular pedicle relative to the muscle's origin and insertion greatly determines the arc of rotation. The closer the dominant vascular pedicle is to either the origin or insertion of the muscle, the greater the arc of rotation. The point of rotation for types I, II, III, and V muscles generally are located at one end or the proximal third of the muscle. For example, type V muscles, such as the pectoralis major and latissimus dorsi, have their major vascular pedicle near their insertion, and correspondingly have a wide arc of rotation. Certain muscles, such as type V muscles, have two arcs of rotation. The first arc of rotation is based on the dominant blood supply, while the second is based on the secondary segmental vascular pedicles. Reverse arc of rotation refers to the degree of transposition of a flap based on its secondary segmental vascular pedicles.

A muscle can be split and a portion in continuity with the dominant vascular pedicle can be used as a transposition flap using just a segment of the muscle. Techniques of muscle splitting to preserve tissue and function have been described. The remaining muscle with its origin and insertion is maintained to preserve function. Alternatively, the entire muscle may be split and used to cover two defects simultaneously. Frequently, only a part of the muscle in proximity to the dominant vascular pedicle is elevated for microvascular transplantation. The skin territory may also be modified and split into two separate skin islands or elevated with only a segment of the muscle flap. However, the skin territory must include vascular connections via musculocutaneous perforating vessels from the segmental flap (Figs. 22.9 & 22.10).

The basis for splitting the pectoralis major muscle was demonstrated by Tobin in 1985.⁴³ The pectoralis has three segmental neurovascular subunits: the clavicular, the sterno-costal, and the external subunit. These can be surgically split and independently transferred on vascular pedicles from the thoracoacromial, internal mammary and lateral thoracic vessels.⁴⁴ Splitting of the pectoralis major muscle into segments has been performed when the segmental transfer of a single intercostal portion of the pectoralis muscle, based on a single medial perforating branch of the internal thoracic artery, is required for chest wall and neck reconstruction (Figs. 22.11 & 22.12).⁴⁵ The concept of segmental transposition of muscle allows transplantation of independent neuromuscular units (segments of muscle innervated by a single nerve fascicle).⁴⁶

Selection of the most appropriate reconstructive method can be difficult. Careful consideration must be given to all the possible methods of repair, and the advantages and disadvantages of each technique must be weighed accordingly.

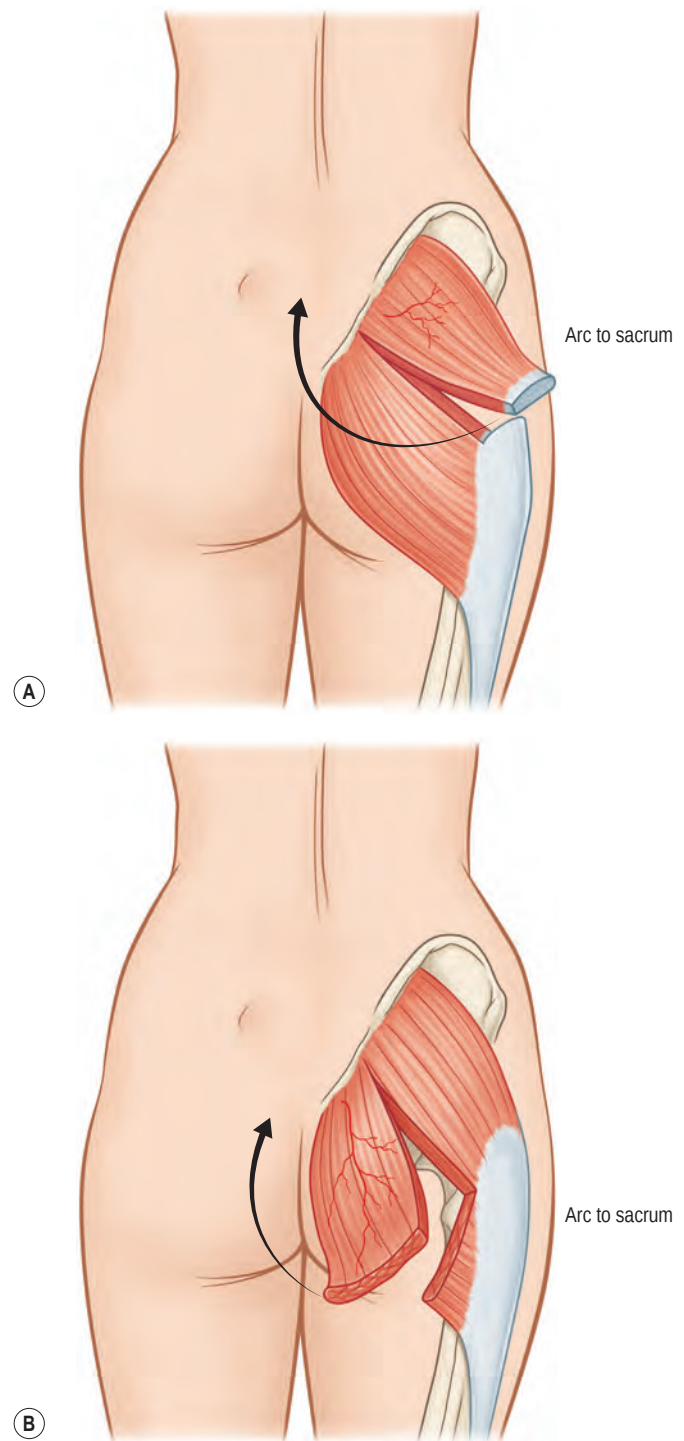


Fig. 22.9 Gluteus maximus segmental muscle transposition. (A) Superior half of gluteus maximus, arc to sacrum. (B) Inferior half of gluteus maximus muscle.

The advantages of muscle or musculocutaneous flaps include the following:

1. The vascular pedicles are specific and reliable.
2. The vascular pedicle is often located outside the surgical defect, which can be particularly important for wounds with an extensive zone of injury beyond the actual wound (e.g., after irradiation, trauma).

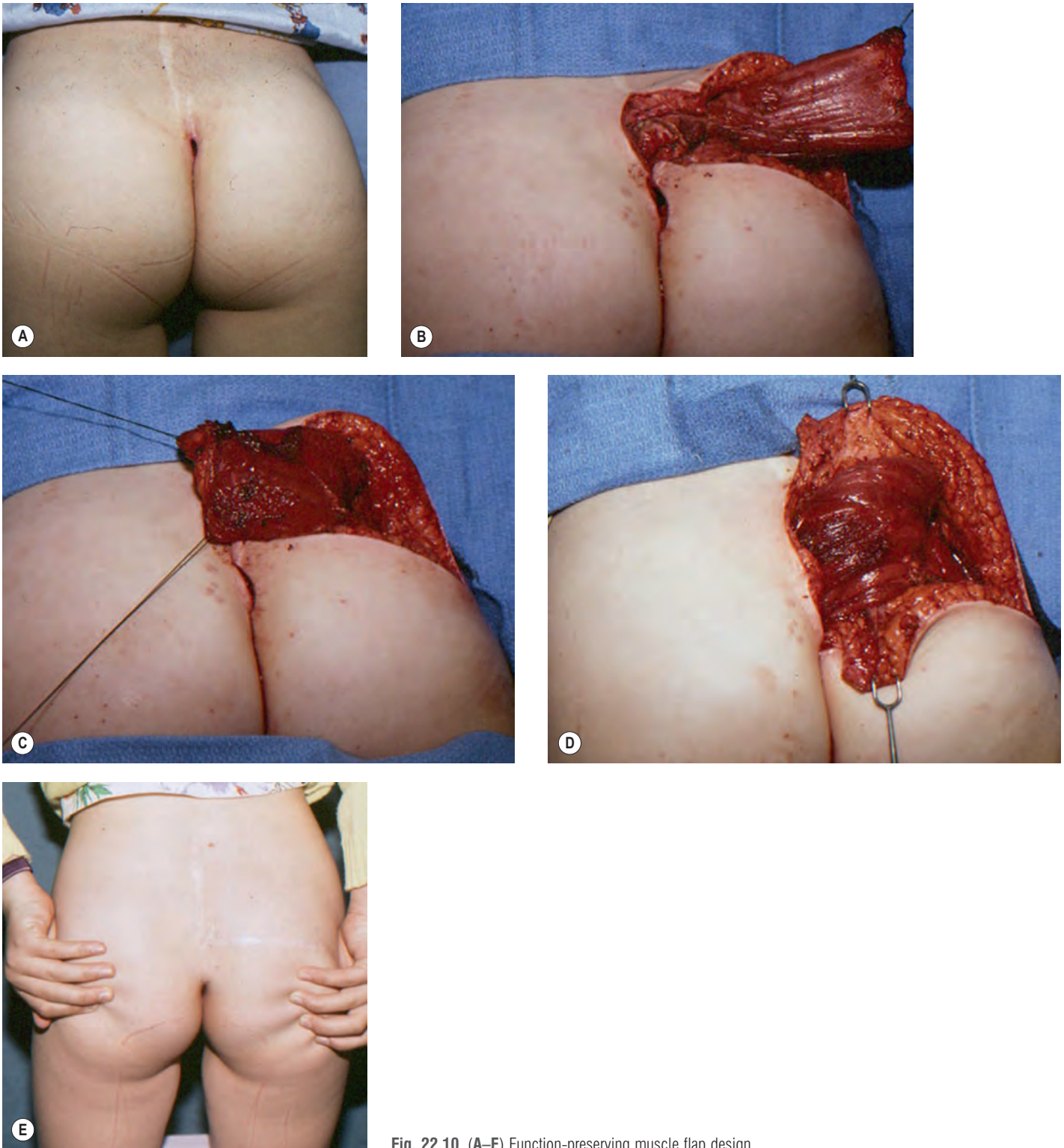


Fig. 22.10 (A–E) Function-preserving muscle flap design.

3. The muscle provides bulk for deep, extensive defects and protective padding for exposed vital structures (e.g., tendons, nerves, vessels, bones, and prostheses).
4. Muscle is malleable and can be manipulated (e.g., folded on itself) to produce a desired shape or volume.
5. Well-vascularized muscle is resistant to bacterial inoculation and infection.⁴⁷
6. Reconstruction by use of muscle or musculocutaneous flaps is often a one-stage procedure.
7. Restoration of function, whether motor or sensory, is possible with certain flaps.
8. The reliability and availability of muscle and musculocutaneous flaps make them an excellent alternative means of reconstruction when the closure

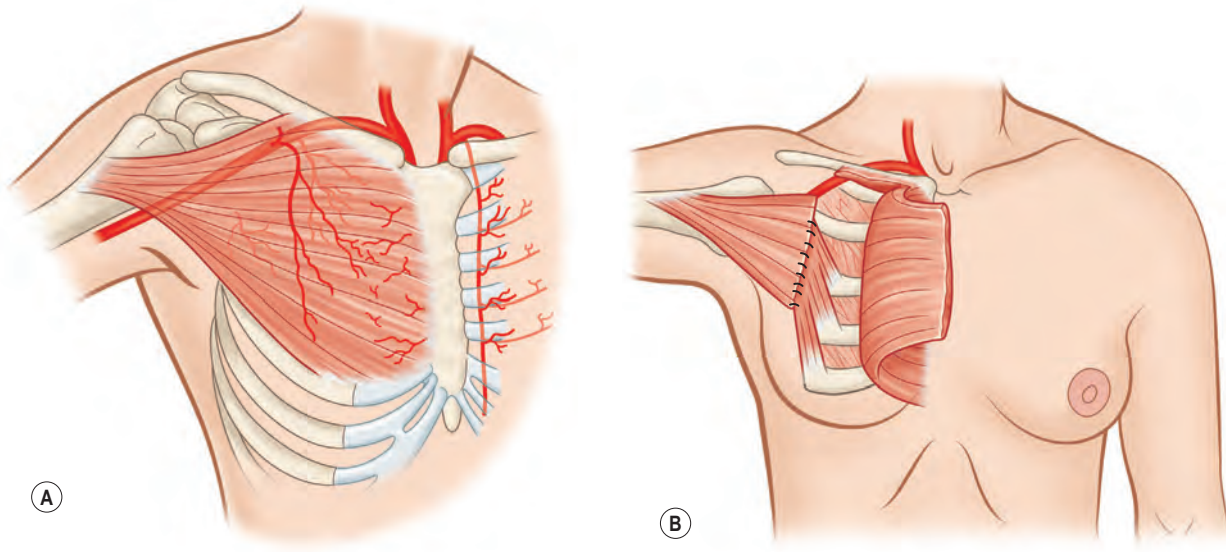


Fig. 22.11 (A,B) Pectoralis major muscle flap segmental transposition.

method of choice for a particular defect is unavailable or inadequate.

The disadvantages of muscle and musculocutaneous flaps include the following:

1. The donor defect may lose some degree of function.
2. The donor defect may be aesthetically undesirable.
3. Reconstruction with muscle or musculocutaneous flaps may provide excessive bulk, leaving an aesthetically unacceptable result.

4. Muscle or musculocutaneous flaps may atrophy over time and thus fail to provide adequate coverage.
5. Removal of the muscle or musculocutaneous flap may result in contour deformities at the donor site.

The preservation of function can be extremely important when nonexpendable muscles are used as flaps. The techniques of function preservation generally involve transposing part of the muscle without completely interrupting the origin or insertion of the donor muscle. For example, the

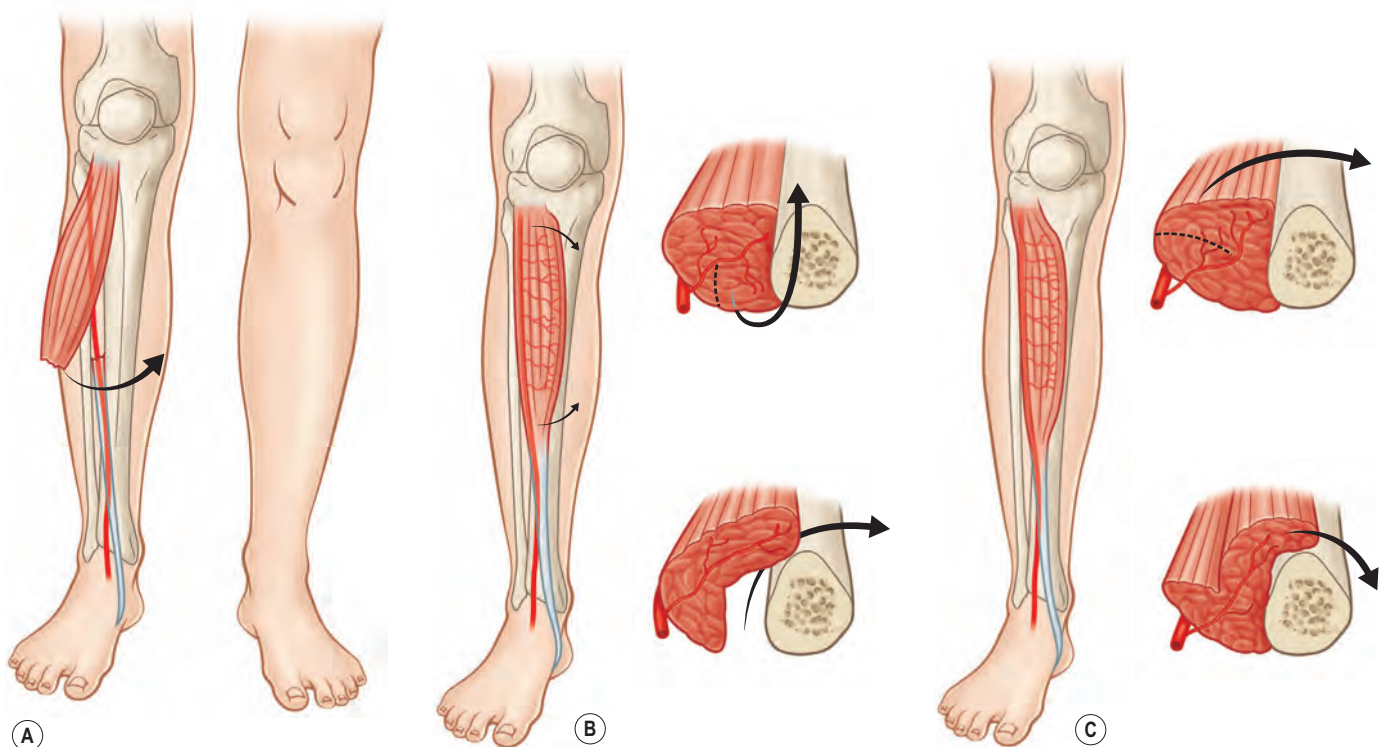


Fig. 22.12 Tibialis anterior muscle flaps split for segmental transposition. (A) Segmental flap. (B) Posterior advancement. (C) Anterior turnover flap.

transposition of the superior half of the gluteus maximus muscle for sacral coverage in the ambulatory patient can be performed without loss of thigh extension or hip stability because the remainder of the gluteus maximus is functionally intact.^{48,49}

Fascia and fasciocutaneous flaps

A growing knowledge of the source of skin circulation after the recognition of the muscle and musculocutaneous system led to the identification of vascular pedicles emerging between muscles (septocutaneous pedicles) and entering the deep fascia. Elevation of the skin with its deep fascia represented a new vascular basis for flap design.

A fascial flap consists of fascia detached from its normal origin or insertion and transposed to another location. Without the overlying skin and fat, this represents a delicate flap. A fasciocutaneous flap, originally called an axial flap, includes the skin, subcutaneous tissue, and underlying fascia, which may be distinct from the fascia covering the underlying muscle. The vascular supply is derived at the base of the flap from musculocutaneous perforators or direct septocutaneous branches of major arteries.

The first fascia and fasciocutaneous flaps were described by Ponten in 1981 for lower extremity reconstruction and Tolhurst in 1983 for trunk and axillary reconstruction.^{23,28} Investigations have shown that the fasciocutaneous system consists of perforating vessels that arise from regional arteries and pass along the fibrous septa between muscle bellies or muscle compartments. The vessels then spread out at the level of the deep fascia, both above and below, to form plexuses, which in turn give off branches to the skin. In 1975, Schafer found three major vascular systems of the deep fascia.⁵⁰

1. Perforating arteries from underlying muscle giving off several radiating branches, which perforate the fascia before continuing to the subdermal plexus.
2. Subcutaneous arteries running in the fat and anastomosing frequently with the superficial plexus of the deep fascia and with each other.
3. Subfascial arteries arising from the intermuscular septa and running in the loose areolar tissue beneath the deep fascia and adjoining the deep and superficial plexus.

These pedicles consist of an artery (generally a branch of the artery to the specific anatomic region of the fascia and regional musculature) and paired venae comitantes that drain into corresponding major regional veins. Direct cutaneous and septocutaneous pedicles are fairly constant in location. There is a greater variability in location of the musculocutaneous perforators. These pedicles provide a vascular basis for specific fascial or fasciocutaneous flaps. On this basis, Mathes and Nahai have classified fascia and fasciocutaneous flaps as types A, B, and C (Fig. 22.13).²⁶

Anatomic studies demonstrate that type A fasciocutaneous flaps have a vascular pedicle to the deep fascia that emerges from a regional source coursing initially beneath the deep fascia and eventually continuing its course superficial to the deep fascia. This pedicle provides numerous fasciocutaneous perforators to the skin. Because the pedicle tends to course in a radial fashion from its regional source into its distal cutaneous distribution, the flap is often referred to as an axial flap. The long, relatively superficial course of the dominant

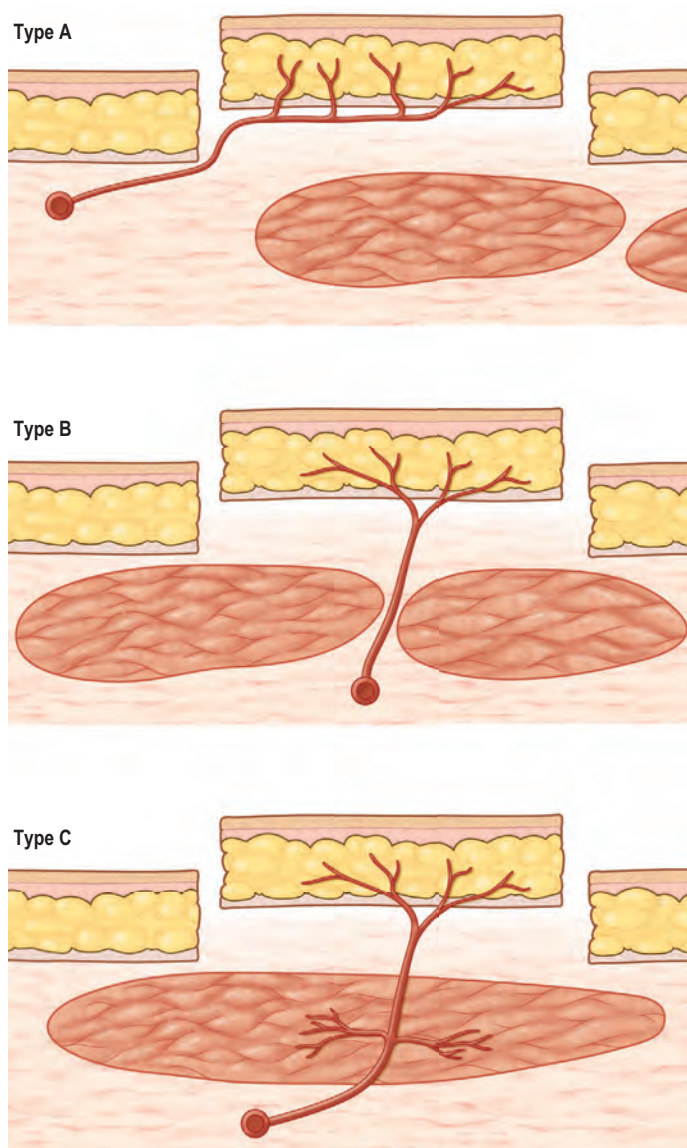


Fig. 22.13 Mathes-Nahai classification of fascia/fasciocutaneous flaps.

pedicle permits evaluation by palpation or Doppler probe (Table 22.8).

Type B fasciocutaneous flaps have a septocutaneous pedicle, which courses between major muscle groups in an intermuscular septum or between adjacent muscles. This pedicle is located within the intermuscular septum or the potential space between adjacent muscles and supplies a regional fascial vascular system. The largest septocutaneous pedicles are dominant pedicles to specific fasciocutaneous flaps and are fairly constant in location (Table 22.9).

In certain regions, larger musculocutaneous perforators enter the deep fascia and contribute to both the deep fascia and cutaneous circulation. The design of a fasciocutaneous flap can be based on these dominant perforating vessels without incorporation of the underlying muscle; this vascular pattern represents the type C fasciocutaneous flap. However, increasing pedicle length will necessitate proximal dissection of the pedicle through muscle to its regional source or incorporation of all or part of the muscle in the flap design. Type

C flaps are generally the anatomic model used for the perforator flap in microsurgical transplantation (Table 22.10).

Cormack and Lamberty also classified fasciocutaneous flaps based on vascular anatomy.^{29,40} The type A flap is supplied by multiple fasciocutaneous perforators that enter at the base of the flap and extend throughout the longitudinal length. The flap can be based proximally, distally, or as an island. The type B flap has a single fasciocutaneous perforator, which is of moderate size and is fairly consistent. It is intended for use as a free flap. The type C flap is based on multiple small perforators that run along a fascial septum.

Table 22.8 Type A fascial and fasciocutaneous flaps

Deep external pudendal artery
Digital artery
Dorsal metacarpal artery
Gluteal thigh
Great toe (hallux)
Groin
Lateral thoracic (axillary)
Pudendal – thigh
Saphenous
Scalp
Second toe
Standard forehead
Superficial external pudendal artery
Superficial interior epigastric artery
Sural artery
Temporoparietal fascia

Table 22.9 Type B fascial and fasciocutaneous flaps

Anterolateral thigh
Anterior tibial artery
Deltoid
Dorsalis pedis
Inferior cubital artery (antecubital)
Lateral arm
Lateral plantar artery
Lateral thigh
Medial arm
Medial plantar artery
Medial thigh
Peroneal artery
Posterior interosseous
Posterior tibial artery
Radial forearm
Radial recurrent
Scapular
Ulnar recurrent

Table 22.10 Type C fascial and fasciocutaneous flaps

Anterolateral thigh
Deltpectoral
Nasolabial
Median forehead
Thoracoepigastric (transverse abdominal)
Transverse back

The supplying artery is included within the flap. It may be based proximally, distally, or as a free flap. The type D flap is an osteomusculofasciocutaneous flap, and is based on multiple small perforators similar to the type C flap, but also includes a portion of adjacent muscle and bone. It may be based proximally or distally on a pedicle or used for microvascular tissue transplantation (Fig. 22.14).

Nakajima *et al.* expanded the types of fasciocutaneous flaps and described them originating from 6 different types of perforators piercing the deep fascia feeding to the plexus of the skin (Fig. 22.15).³⁷ Type A, direct cutaneous branch of muscular vessel was described in the same manner as axial pattern flaps of McGregor and Morgan.⁵¹ Type B, septocutaneous perforator was the same as type B from the classification of Cormack and Lamberty.⁴⁰ Type C, direct cutaneous branch and type D, musculocutaneous perforator supplying the fasciocutaneous flap were not quite described in previous classifications. These types, especially type D from the Nakajima *et al.* classification, further play a pivotal role for setting up the concept of true perforator flaps.⁵² Type E, direct septocutaneous describes type C from the classification of Cormack and Lamberty and type F, perforating cutaneous branch of muscular vessel resembles traditional musculocutaneous flaps.^{22,29,40}

The fasciocutaneous flap is used as a local flap, the standard arc of rotation is determined by the extent of elevation of the deep fascia from its normal anatomic position to reach adjacent defects. The point of rotation is based on the site of entrance of the dominant vascular pedicle into the fascia. The fascia or fasciocutaneous flap is elevated to the point of entrance of the flap pedicle, and the fascia and overlying skin distal to this point are rotated into the defect.

The advantages and disadvantages of these flaps are somewhat similar to those of muscle flaps, although there are a few exceptions. The advantages include the following:

1. They are thin and pliable.
2. The blood supply is reliable and robust.
3. The donor site morbidity is minimal in regard to function.
4. They are muscle sparing.
5. They have the ability to restore sensation.
6. There are many potential donor sites.

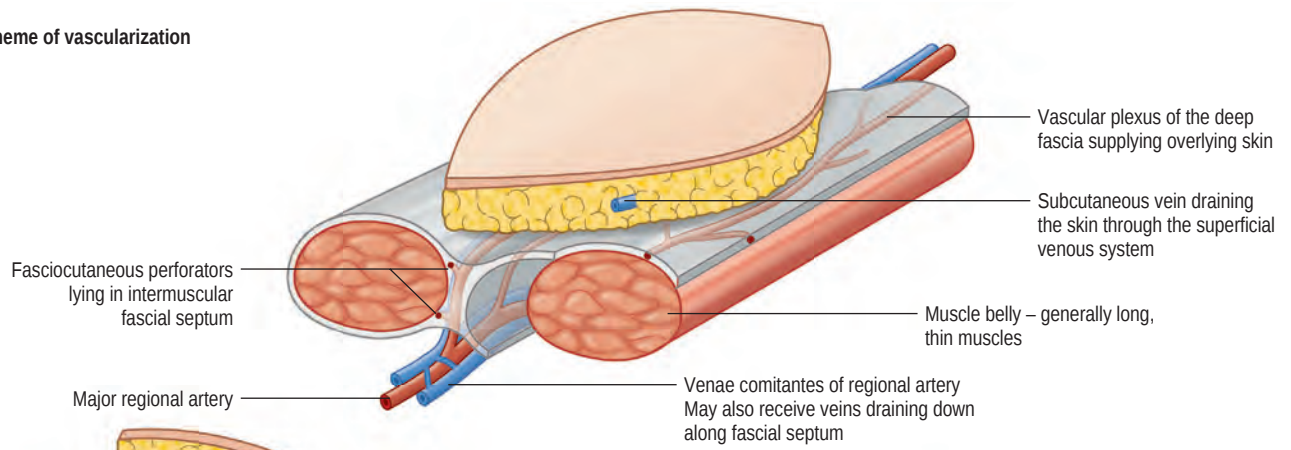
The disadvantages of fascia, fasciocutaneous, and perforator flaps include the following:

1. There is a lack of bulk for deep defects.
2. They are technically more challenging (pedicle dissection; many require microvascular anastomosis or at least microvascular techniques).
3. There are size limitations.
4. The arc of rotation is sometimes limited though often better than the similar muscle flap because of the longer pedicle.
5. Donor site may require skin graft closure, resulting in donor site deformity.

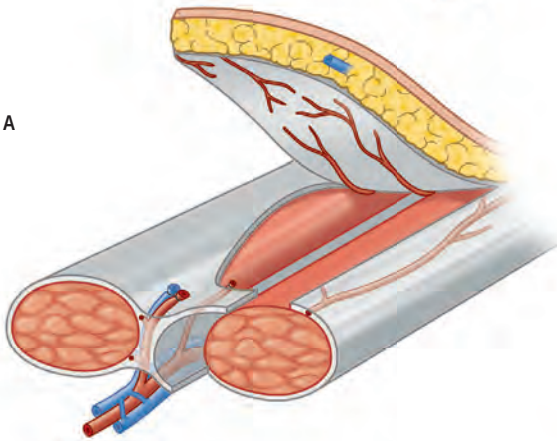
Perforator flap (skin with fat and with or without fascia)

Further refinements in flap application have led to the development of perforator flaps. Perforator flaps have evolved

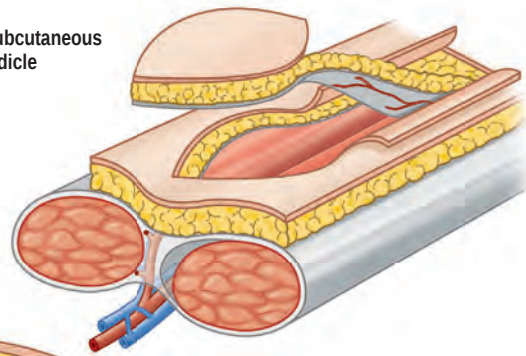
General scheme of vascularization



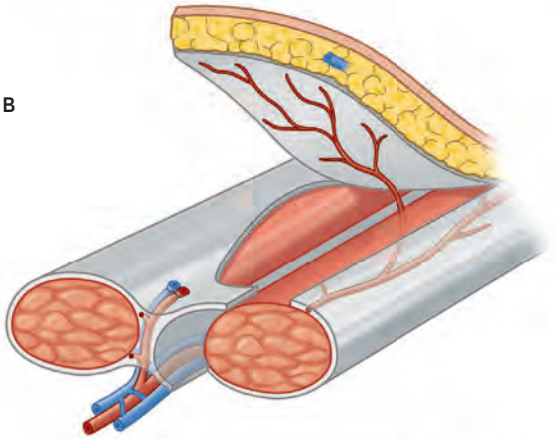
Type A



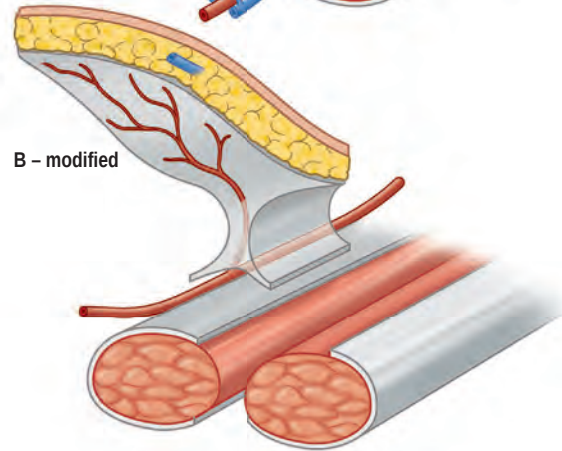
Type A – Subcutaneous pedicle



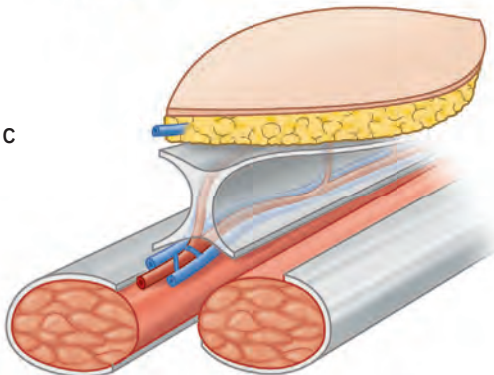
Type B



B – modified



Type C



Type D

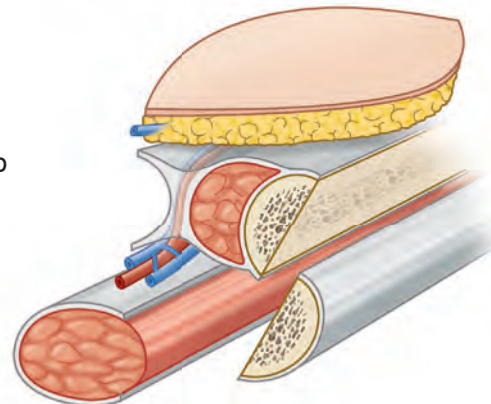


Fig. 22.14 Classification of fasciocutaneous flaps.

from musculocutaneous and fasciocutaneous flaps without the muscle or fascial carrier. It was a natural evolution as reconstruction needed fine-tuning while aiming to minimize donor morbidities. A good example of this evolution would be the change from transverse rectus abdominis muscle (TRAM) flaps to muscle-sparing TRAM to deep inferior epigastric perforator (DIEP) flaps (Fig. 22.16). Transformation of these flaps has shown that neither a passive muscle carrier nor the underlying fascial plexus of vessels are necessary for flap survival.⁵³ Thus, a perforator flap is a skin flap (with or without fascia) based on a single perforator.⁵⁴ Like the angiosome concept showing the vascular territory of a source vessel, one must understand the anatomy and physiology of a single perforator territory to obtain the ideal design of the perforator flap.³³ The perforasome theory by Saint-Cyr reported four major characteristics of a perforator flap: (1) each perforasome is linked with adjacent perforasomes by means of direct and indirect linking vessels (Fig. 22.17); (2) flap design and skin paddle orientation should be based on the direction of the linking vessels, which is axial in the extremities and perpendicular to the midline in the trunk (Fig. 22.18); (3) filling of the perforasomes occurs within perforasomes of the same source artery first followed by perforators of the other adjacent source arteries; (4) mass vascularity of a perforator found adjacent to an articulation is directed away from that same articulation (Fig. 22.19).³⁸ This theory provides insights into perforator flap vascularity and can clinically guide to the harvest of a safer free or pedicle perforator flap.

In 1989 Koshima and Soeda used the term “perforator flaps” in their harvest for paraumbilical skin and fat island flaps based on a muscular perforator.⁵³ Since then, perforator-based flaps using lower abdomen skin flaps have been applied for breast reconstruction.^{55,56} Slowly other perforator-based flaps have been introduced from various parts of the skin.

The nomenclature of perforator flaps is confusing and oftentimes misstated. Perforator flaps have been designated by their location (e.g., anterolateral thigh flap), arterial supply (e.g., deep inferior epigastric artery perforator flap), or the muscle of origin (e.g., gastrocnemius perforator flap). Thus, a

clear definition and classification for perforator flaps was needed. Hallock defines a perforator as any vessel that pierces through the fenestration in the deep fascia regardless of origin.⁵⁴ In a consensus document for perforator flap terminology, perforators that pierce through the deep fascia without traversing any other structural tissues were called direct perforators while indirect perforators run through deeper

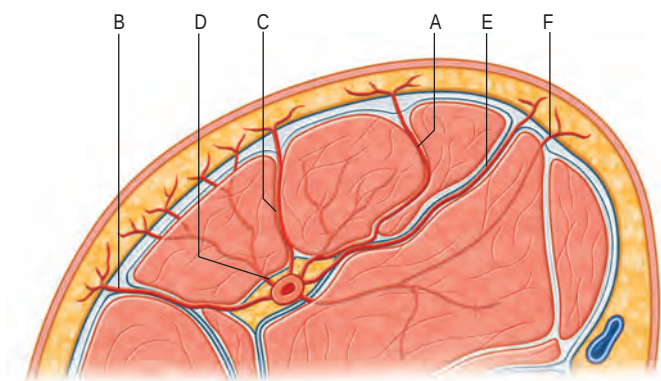


Fig. 22.15 The six distinctive deep fascia perforators according to Nakajima and colleagues are indicated. A, direct cutaneous branch of a muscular vessel; B, septocutaneous perforator; C, direct cutaneous; D, musculocutaneous perforator; E, direct septocutaneous; F, perforating cutaneous branch of a muscular vessel. A separate type of fasciocutaneous flap could be named after each different perforator. (Modified from Nakajima H, Fujino T, Adachi S. A new concept of vascular supply to the skin and classification of skin flaps according to their vascularization. *Ann Plast Surg.* 1986;16:1–19.)

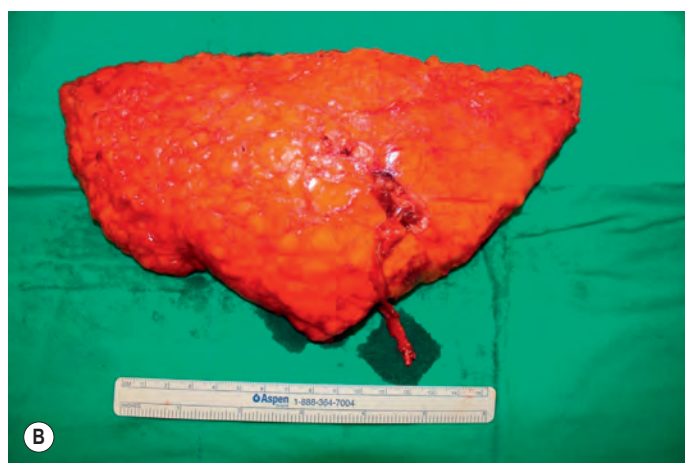


Fig. 22.16 Evolution of the abdominal skin flap for breast reconstruction from transverse rectus abdominis muscle (TRAM) flap (A) to muscle-sparing TRAM (B) to deep inferior epigastric perforator (DIEP) flaps (C).

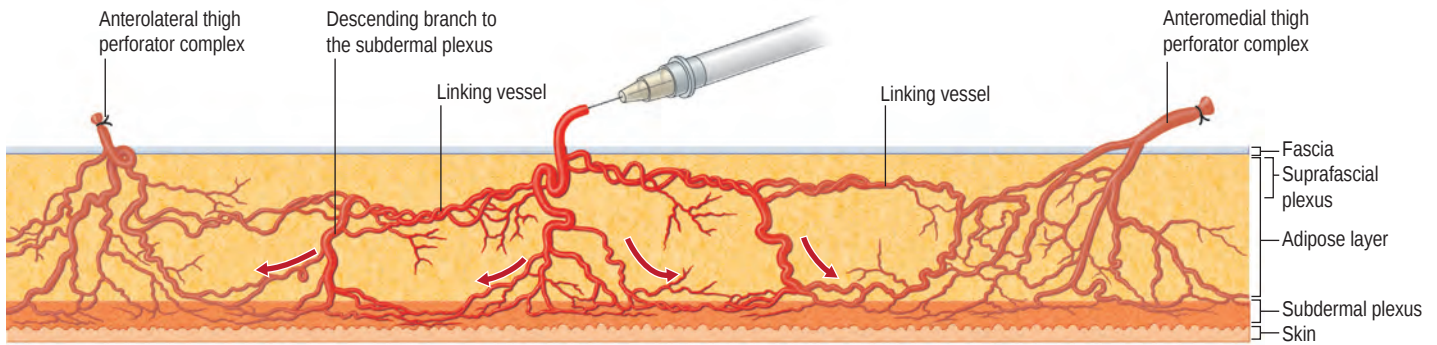
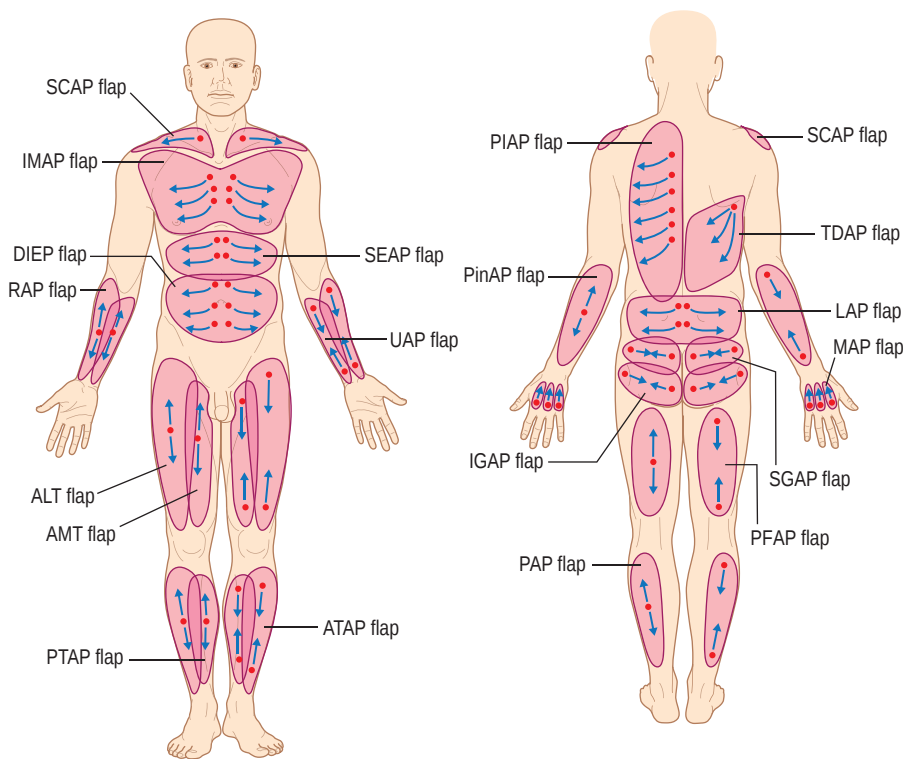


Fig. 22.17 Each perforasome is linked with adjacent perforasomes by means of direct and indirect linking vessels. Direct linking vessels communicate directly with adjacent perforators and indirect linking vessels are communicating through the subdermal plexus.

structures such as muscles, septum and perimysium.^{54,57} Evolved from the six patterns of fascial perforators of Nakajima *et al.*, the consensus paper simplified it into 5 types of perforator based on the surgical approach for dissection of the perforators (**Fig. 22.20**). Type 1: direct perforators perforate the deep fascia only; type 2: indirect muscle perforators

predominantly supply the subcutaneous tissues; type 3: indirect muscle perforators predominantly supply the muscle but have secondary branches to the subcutaneous tissues; type 4: indirect perimysial perforators travel within the perimysium between muscle fiber before piercing the deep fascia; type 5: indirect septal perforators travel through the



SCAP Supraclavicular artery perforator
 IMAP Internal mammary artery perforator
 DIEP Deep inferior epigastric perforator
 RAP Radial artery perforator
 ALT Anterior lateral thigh
 AMT Anterior medial thigh
 PTAP Posterior tibial artery perforator
 SEAP Superior epigastric artery perforator
 UAP Ulnar artery perforator
 ATAP Anterior tibial artery perforator

PIAP Posterior intercostal artery perforator
 PinAP Posterior interosseus artery perforator
 IGAP Inferior gluteal artery perforator
 PAP Peroneal artery perforator
 TDAP Thoracodorsal artery perforator
 LAP Lumbar artery perforator
 SGAP Superior gluteal artery perforator
 MAP Metacarpal artery perforator
 PFAP Profundus femoris artery perforator

Fig. 22.18 Orientation of the perforators should be understood and utilized when designing flaps. The skin paddle orientation should be based on the direction of the linking vessels, which is axial in the extremities and perpendicular to the midline in the trunk.

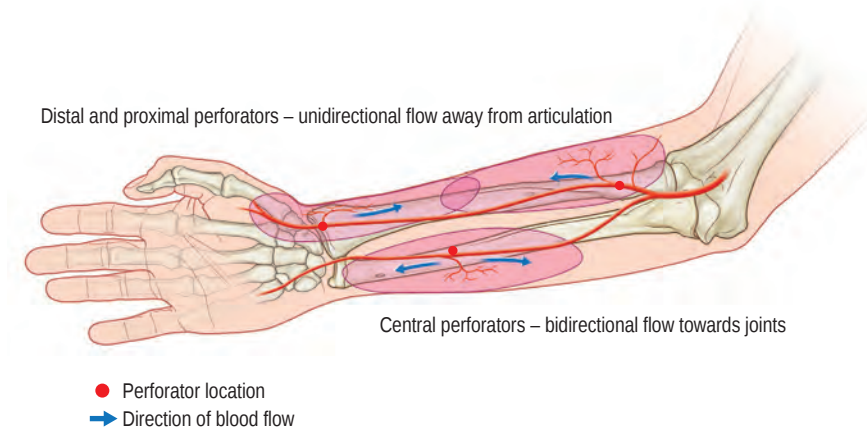


Fig. 22.19 Direction of perforator flow between articulations.

intermuscular septum before piercing the deep fascia. Based on this distinction of different perforators, the consensus paper gives definitions and classification for perforator flaps as follows:

Definition 1: A perforator flap is a flap consisting of skin and/or subcutaneous fat. The vessels that supply the blood to the flap are isolated perforator(s). These perforators may pass either through or in between deep tissues (mostly muscle).

Definition 2: A muscle perforator is a blood vessel that traverses through septum to supply the overlying skin.

Definition 3: A septal perforator is a blood vessel that traverses only through septum to supply the overlying skin.

Definition 4: A flap that is vascularized by a muscle perforator is called a muscle perforator flap.

Definition 5: A flap vascularized by a septal perforator is called a septal perforator flap.

Definition 6: A perforator flap should be named after the nutrient artery or vessels and not after the underlying muscle. If there is a potential to harvest multiple perforator flaps from one vessel, the name of each flap should be based on its anatomical region or muscle.

This terminology and the classification into indirect and direct perforator flaps and further into septal and muscle perforator flaps were set up to clearly identify the course of these small terminal branches before they pierce the deep fascia and the technical implications during the surgical procedure.^{57,58} Table 22.11 shows some of the popular perforator flaps based on this terminology. Recent innovations in this field have made some of the terminology and classification somewhat misleading. As with all evolution, new classification and terminology will be constantly updated.

The perforator flap concept simplified and overcame the applications and limits of classic local flaps. By identifying the perforator as the pedicle and further dissecting toward the source vessel, it allowed improved movement and better survival of flap. One form of perforator-based local flap, the propeller flap, is an island flap that reaches the recipient site through an axial rotation.^{59,60} When a perforator propeller flap is being elevated, the perforator is dissected free from the fascial and fat adhesions to minimize the chance of kinking. Although less rotation reduces the chance for kinking, the skin island may be safely rotated up to 180° (Fig. 22.21).

Advantages of perforator flaps include:

1. Reduced donor site morbidity
2. Versatility in flap design
3. Muscle sparing (less functional deficit)
4. Improved postoperative recovery of the patient.^{61–65}

Disadvantages of perforator flaps may include:

1. Meticulous dissection needed to isolate the perforator vessels
2. Increased operative time especially in muscle perforators
3. The variability in the position and size of the perforator vessels
4. Steep learning curve.^{66,67}

However, modifications such as the free-style approach and supermicrosurgery have further simplified the approach and increased the use of perforator flaps.^{68–70} The free-style

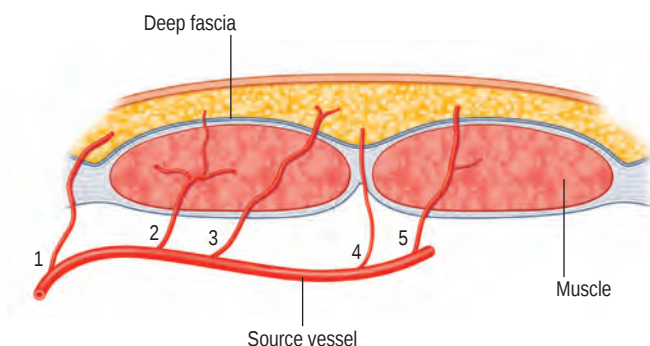


Fig. 22.20 The different types of direct and indirect perforator vessels with regard to their surgical importance. 1, Direct perforators perforate the deep fascia only; 2, indirect muscle perforators predominantly supply the subcutaneous tissues; 3, indirect muscle perforators predominantly supply the muscle but have secondary branches to the subcutaneous tissues; 4, indirect perimysial perforators travel within the perimysium between muscle fibers before piercing the deep fascia; 5, indirect septal perforators travel through the intermuscular septum before piercing the deep fascia. (Adapted from Blondeel PN, Van Landuyt KH, Monstrey SJ, et al. The "Gent" consensus on perforator flap terminology: preliminary definitions. *Plast Reconstr Surg*. 2003;112:1378–1383; quiz 1383, 1516; discussion 1384–1387.)

Table 22.11 Perforator flap terminology

Flap – abbreviation	Flap – full name	Nutrient artery
Muscle perforator flaps		
DIEP	Deep inferior epigastric perforator	Deep inferior epigastric vessels
TAP	Thoracodorsal artery perforator	Thoracodorsal vessels
SGAP	Superior gluteal artery perforator	Superior gluteal vessels
IGAP	Inferior gluteal artery perforator	Inferior gluteal vessels
IMAP	Internal mammary artery perforator	Internal mammary vessels
ICAP	Intercostal perforator	Intercostal vessels
PLP	Paralumbal perforator	Paralumbal perforating vessels
GP	Gracilis perforator	Medial circumflex femoris vessels
TFLP	Tensor fasciae latae perforator	Transverse branch of the lateral circumflex femoris vessels
ALTP	Anterolateral thigh perforator	Descending branch of the lateral circumflex femoris vessels
AMTP	Anteromedial thigh perforator	Innominate branch of the descending branch of the lateral circumflex femoris vessels
SAP	Sural artery perforator	Sural vessels
PTAP	Posterior tibial artery perforator	Posterior tibial vessels
ATAP	Anterior tibial artery perforator	Anterior tibial vessels
Septal perforator flaps		
RAP	Radial artery perforator	Radial vessels
AP	Adductor perforator	Medial circumflex femoris vessels
AMTP	Anteromedial thigh perforator	Innominate branch of the descending branch of the lateral circumflex femoris vessels (if perforator runs only in septum)
ALTP	Anterolateral thigh perforator	Descending branch of the circumflex femoris lateralis vessels (if perforator runs only in the septum)

(From Blondeel PN, Van Landuyt KH, Monstrey SJ, et al. The “Gent” consensus on perforator flap terminology: preliminary definitions. *Plast Reconstr Surg*. 2003;112:1378–1383; quiz 1383, 1516; discussion 1384–1387.)

approach identifies the perforator feeding the skin flap first and then dissects proximally toward the source vessel contrary to the classic approach where identification of the source vessel was made first and then dissection toward the perforator. This allows the freedom to design flaps based on any perforator as well as alleviate the risk for pedicle variation.⁶⁸ The supermicrosurgery approach, perforator to perforator anastomosis, allows harvesting the flap as a short pedicled flap, reducing the dissection time and minimizing the risk for traumatizing the pedicle during dissection.^{69,71}

Visceral flaps

The abdominal viscera are not easily classified; however, for the purposes of flap transposition or microvascular tissue transplantation, the colon, jejunum, and omentum fall conveniently into the muscle classification system (Table 22.12). For microvascular transplantation, the segment of bowel (jejunum or colon) is elevated on one vascular arcade with a single dominant vessel, a type I pattern of circulation. In unusual circumstances where a longer segment of bowel extends beyond the vascular territory of one arcade, two vascular arcades must be included to ensure viability of this longer segment of bowel. In this instance, the pattern of circulation will be type III (two dominant arcades or pedicles). It is possible to reconstruct the esophagus from the base of the tongue

to the stomach with a long segment of jejunum where one pedicle is revascularized in the upper chest or neck and the second pedicle is left intact. Additional uses of the colon or jejunum as flaps have been for vaginal reconstruction. The appendix, as a type I pattern based on the appendiceal artery and vein, has been used for reconstructing the urethra and for voice reconstruction.^{72–74}

Table 22.12 Abdominal visceral flap classification

Flap	Type	Circulation pattern	Size
Colon	Bowel	Type I	20–25 cm in length Lumen diameter of 8 cm
Jejunum	Bowel	Type I	7–25 cm may be transferred on one pedicle Lumen diameter of 3–5 cm
Omentum	Omentum	Type III	Variable; up to 40×60 cm

The omentum may be based as a transposition flap on either the right or left gastroepiploic vessels and is thus classified as having a type III pattern of circulation. The omentum is also commonly transferred microsurgically. The omentum can be used to reconstruct a wide range of extraperitoneal defects and has been shown to have immunologic and angiogenic properties.⁷⁵⁻⁷⁷ Although useful for reconstruction, donor site complications can be significant, including abdominal wall infection and hernia.^{78,79} With the advances in minimally invasive surgery, the abdominal viscera can successfully be harvested laparoscopically obviating the need for a large midline incision providing a better cosmetic result and less donor site morbidity.^{31,80,81}

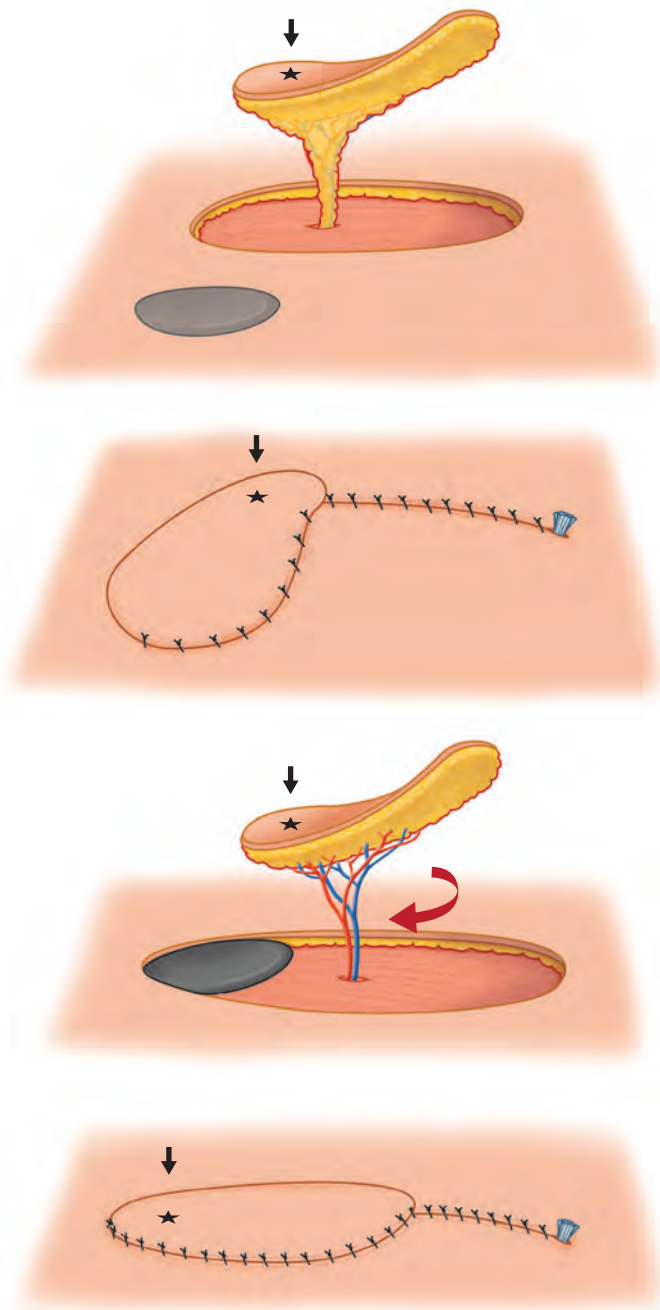


Fig. 22.21 One form of perforator-based local flap, the propeller flap, is an island flap that reaches the recipient site through an axial rotation.

Bone flap (vascularized bone, osseous–periosteal flap)

Bone is vascularized through endosteal and periosteal sources (Fig. 22.22). The complex blood supply of bone is based on nutrient vessels entering the bone directly and through vascular connections between muscles and bone, typically where the muscle has a large bony origin or insertion. Vascularized bone is useful in muscles suitable for microvascular transplantation or in those muscles designed for transposition when the vascular attachments to bone are distal to the point of rotation. The commonly transferred bones include the fibula based on the peroneal artery, iliac crest based on the deep circumflex iliac artery (Fig. 22.23), the scapula based on the circumflex scapula or thoracodorsal arteries (Fig. 22.24), and the radius based on the radial artery (Fig. 22.25). The calvarial osseous flap based on the superficial temporal artery or occipital artery with partial- or full-thickness bone is also useful for reconstructing facial anomalies and deformities (Fig. 22.26).⁸²⁻⁸⁵

The use of periosteum and part of the cortical bone as an osseous–periosteal flap is being widely used for nonunion of the bone and small bone defects. The genicular osseous–periosteal flap, also known as the medial femoral condyle flap, based on the articular branch of the descending genicular artery and vein with periosteum and a thin (0.5 to 1.0 mm) layer of outer cortical bone, was first reported by Sakai *et al.* to treat fracture nonunion (Fig. 22.27).⁸⁶ Further applications of this flap with or without skin and cartilage expanded to reconstructing small bone defects, avascular necrosis of the bone and other complex defects of the hand.⁸⁷⁻⁸⁹

There is no widely accepted classification of bone flaps alone. Perhaps it is due to the complexity of the vasculature to each bone. One of the most widely used, the fibula, has vascular supply from the branches of the anterior tibial artery supplying the head, neck, and epiphysis while the peroneal

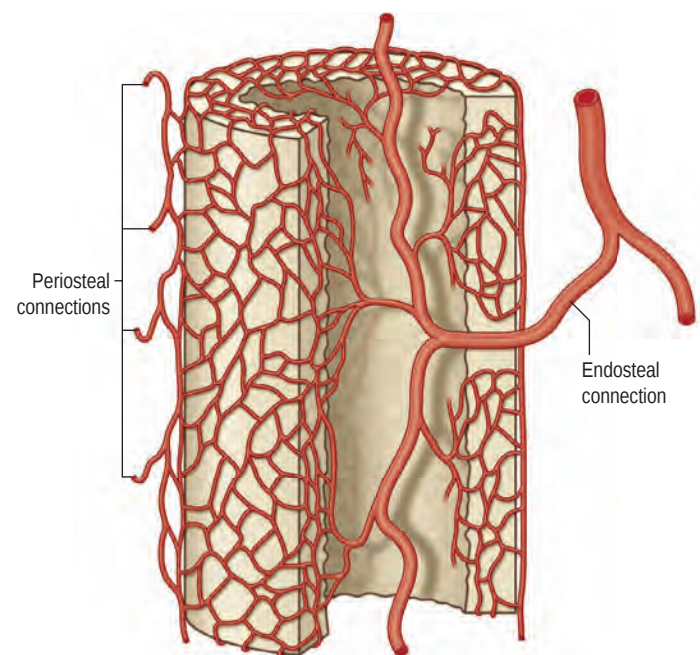


Fig. 22.22 Flap vascular connections to bone.

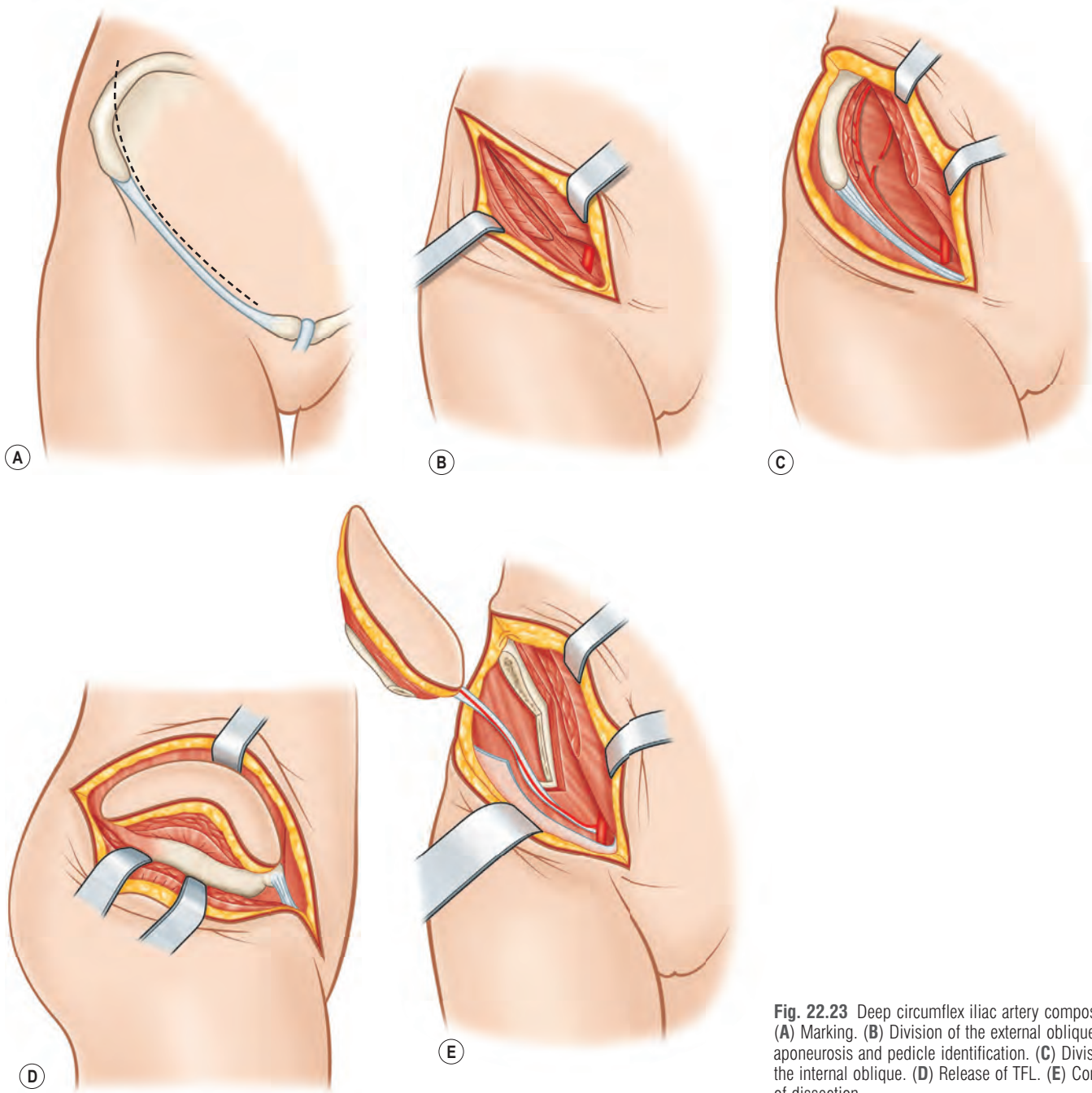


Fig. 22.23 Deep circumflex iliac artery composite flap. (A) Marking. (B) Division of the external oblique aponeurosis and pedicle identification. (C) Division of the internal oblique. (D) Release of TFL. (E) Completion of dissection.

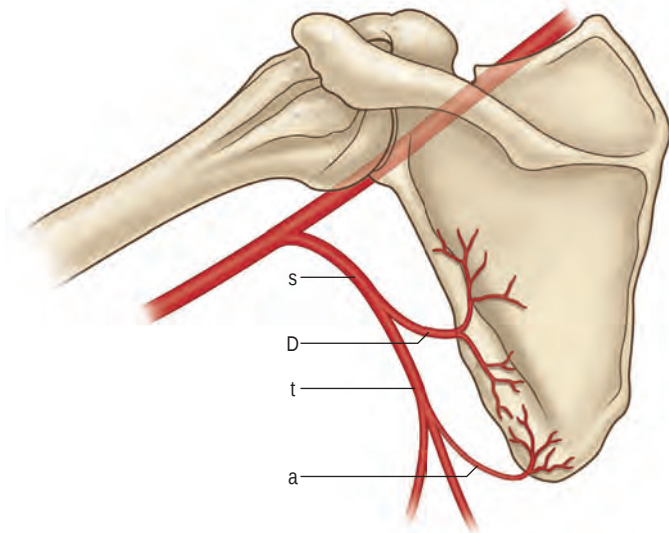


Fig. 22.24 Independent vascularized segments of the scapula based on circumflex scapular and thoracodorsal pedicles. s, subscapular artery; D, circumflex scapular artery; t, thoracodorsal artery; a, scapular arterial branch.

artery gives rise to multiple arcuate vessels along the fibula and a nutrient vessel in the mid third of the fibula bone (Fig. 22.28). Thus, depending on the portion of the fibula bone being harvested, the pedicle of the bone flap can differ not only in anatomical region but also in type of vascular supply to the bone. The fibula bone flap with or without the skin (fasciocutaneous) flap is frequently used for segmental bone defects especially after mandibular resection, long bone resection and for pelvis reconstruction (see Fig. 22.23).⁹⁰ The fibular bone including the head and epiphyseal growth plate is used in patients who need further growth of the long bone such as reconstruction after sarcoma resection of the proximal humerus.^{91,92}

Nerve flap

The sensory nerves are supplied by an extrinsic and intrinsic blood supply. The extrinsic blood supply to the peripheral nerves consists of arteriae nervorum that rise directly from the perforating vessels. These perforating vessels may originate from various deeper vessels as seen from Nakajima's perforator classification.³⁷ These small arteriae nervorum enter the nerve and terminate intraneurally. The intrinsic blood supplies are the longitudinally oriented arterioles located on the epineurium, perineurium, and endoneurium. The intrinsic vessels communicate and receive vascular supply from the extrinsic arteriae nervorum and the end branches (Fig. 22.29).^{93,94} Thus, the nerve flap can be harvested from superficially located sensory nerves based on perforating vessels originating from a proximal source vessel. Based on this clear distinction of tissue being supplied by a vascular source, the term "vascularized nerve graft" would be a misnomer and "nerve flap" should be used to minimize confusion. Currently there is no classification for nerve flaps.

Well-known examples of nerve flaps would be superficial radial nerve flap based on the radial artery and accompanying veins, saphenous nerve flap proximally based on the branches

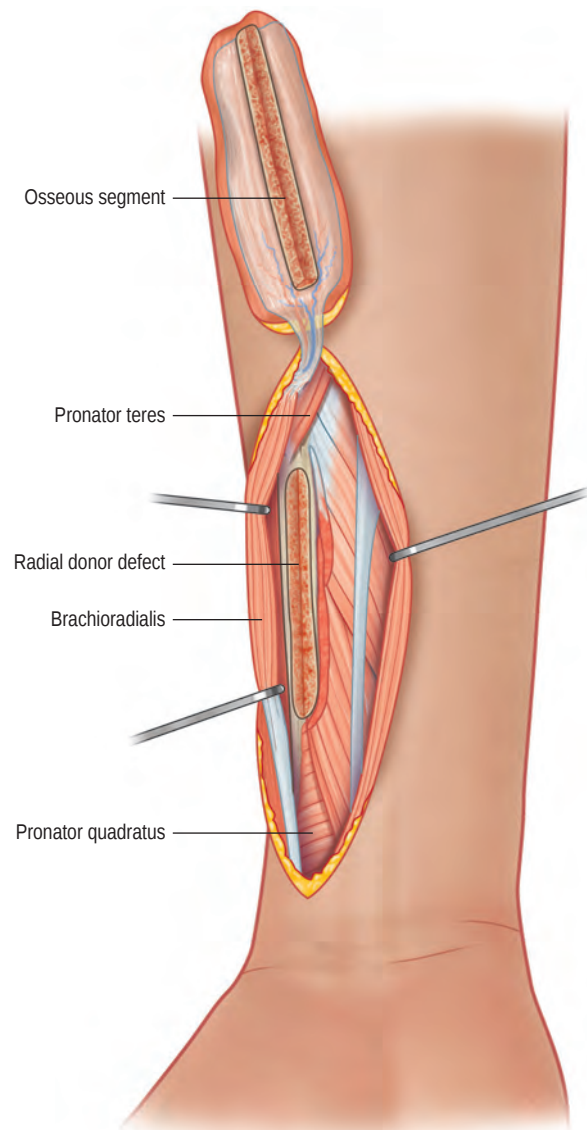


Fig. 22.25 An osteocutaneous flap with composition of radius bone, and attached fasciocutaneous flap is elevated based on the proximal radial artery and vein pedicle.

from the femoral artery and distally based on the saphenous artery, and sural nerve flap based on the superficial sural artery or medial sural artery.⁹⁵⁻⁹⁹

In cases where perforators are not found leading to the superficial nerve, one can use the accompanying vein along the superficial nerve in an arterialized fashion. A typical example would be the sural nerve flap, where an arterial supply such as superficial sural artery, medial or lateral sural artery would be missing and the lesser saphenous vein would be arterialized (Fig. 22.30).¹⁰⁰⁻¹⁰²

Lymph node flap

Each lymph node has afferent lymphatic vessels that transport lymph to the node and an efferent vessel that transports fluid toward the thorax and into the chylothoracic duct. The node itself also has its vascular supply based on arterial inflow and

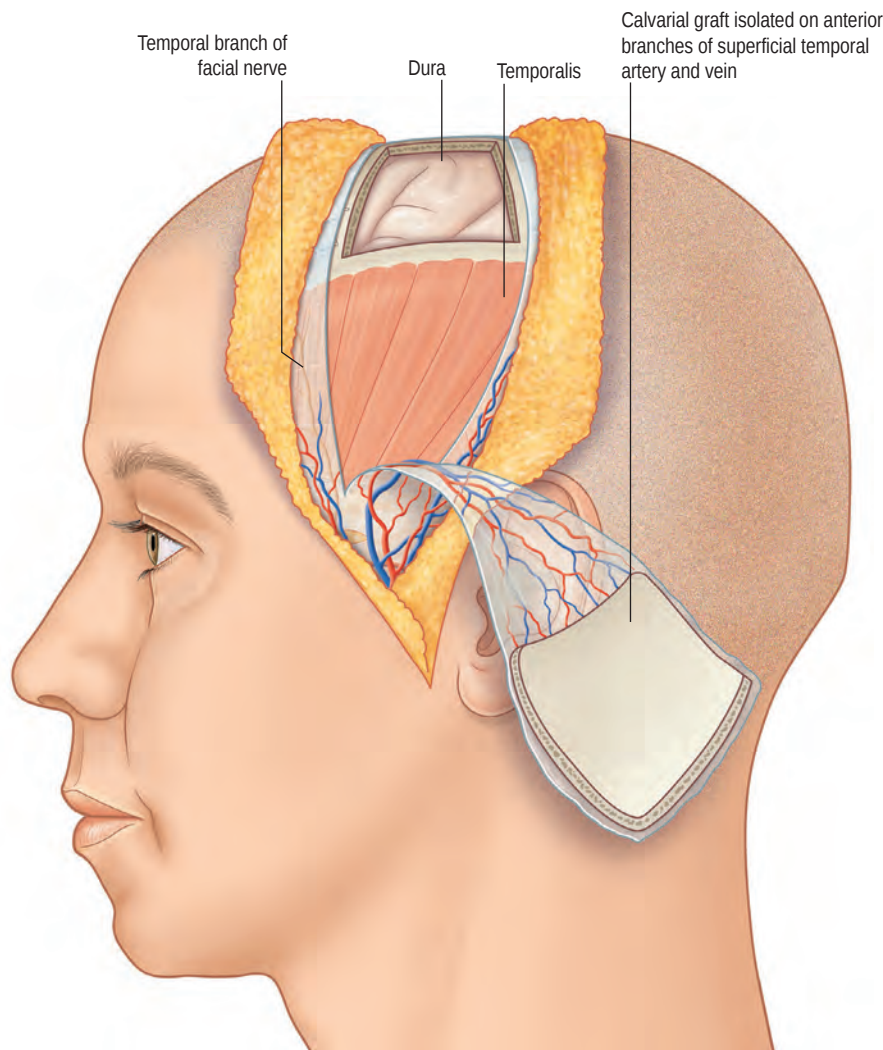


Fig. 22.26 The calvarial osseous flap based on the superficial temporal artery with a segment of temporal fascia and muscle is elevated.

venous outflow (Fig. 22.31). This is why lymph node(s) with fat can be considered as a flap. It is this lymph node flap transfer that offers a solution to lymphedema patients. Often lymph node vessels are extremely small and may require supermicrosurgery technique to anastomose to a recipient vessel but can be anastomosed comfortably when dissected proximally toward the source vessels such as superficial inferior epigastric artery, superficial circumflex iliac artery, and supraclavicular artery.^{103–106} Although the mechanism remains unclear, clinical reports have been encouraging along with lymphovenous shunting for lymphedema.^{106,107}

Flaps based on construction (flow)

For most of the flaps, whether they be muscle or skin or a combination of various tissues, the pedicle usually drains into a single source making unipedicle the most common form. We do not use the term unipedicle as part of the nomenclature but as a default to communicate. The same can be said for antegrade (orthograde) flow. A bipedicle flap is a flap with dual pedicle, often used as a random pattern skin flap to cover a defect on the extremity, or a transabdominal bipedicle flap

can be raised to provide coverage on the dorsum of the hand (Fig. 22.32).

Retrograde-flow flaps

A flap based on the antegrade flow has a major pedicle that flows with the flap but, when the same flap has its orthograde pedicle ligated proximally, becomes a flap based on the distal part of the major pedicle and the flow of the flap becomes reversed (Fig. 22.33A). This concept was first reported by Bostwick *et al.* using a reverse-flow temporal artery island flap.¹⁰⁸ In reality, some of the random pattern flaps or axial cutaneous flaps were used in a reverse manner without realizing the axi-ality and direction of the flow, such as acromio-thoracic tube pedicle.¹⁰⁹

A number of clinically useful retrograde (reverse) flow flaps have been described since its original description in 1976, including the distally based radial forearm fasciocutaneous flap, posterior interosseous flap, and the reversed first dorsal metacarpal artery flap used in hand reconstruction.^{110–112} The distally based radial forearm flap relies on retrograde flow through the deep palmar arch and associated venae

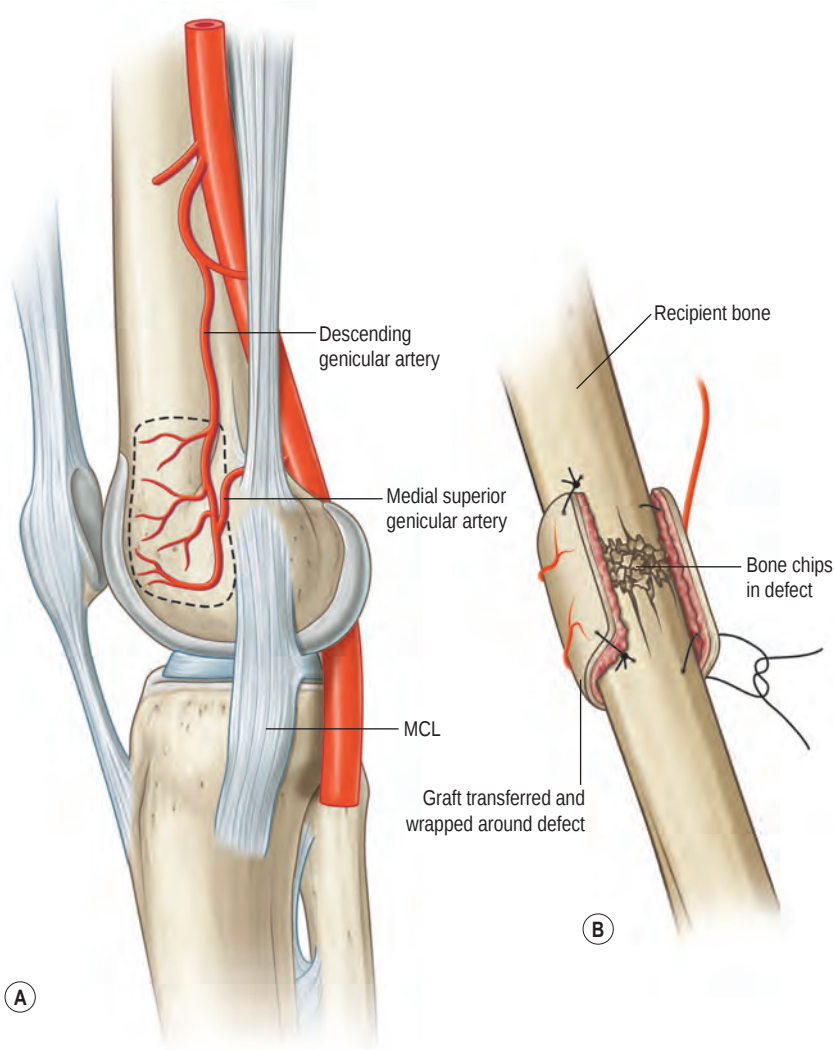


Fig. 22.27 The genicular osseous-periosteal flap, also known as the medial femoral condyle flap, is based on the articular branch of the descending genicular artery and vein with periosteum and thin (0.5–1.0 mm) layer of outer cortical bone (A). It is commonly used to reconstruct small bone defects, avascular necrosis of the bone and other complex defects of the hand (B). MCL, medial collateral ligament.

comitantes with the rotation point of the reverse flap at the level of the wrist (Fig. 22.33B). Examples of reversed flow flaps used for lower extremity reconstruction are sural fasciocutaneous flaps based on perforators from the peroneal artery, lateral calcaneal flaps based on reverse flow of the lateral calcaneal artery and reversed flexor hallucis longus flaps based on retrograde flow through the peroneal artery.^{113–115}

The reverse-flow island sural flap is based on the superficial sural artery. The anatomic structures in the path of the pedicle are superficial and deep fascia, the sural nerve, the short saphenous vein, and the superficial sural artery. The sural nerve usually descends between the two heads of the gastrocnemius muscle and penetrates the deep fascia at the mid leg. The median branch of the superficial sural artery follows the course of the sural nerve and descends to the ankle region anastomosing with the peroneal artery. Thus, when the sural artery and nerve is ligated proximally and the flap is distally positioned, the flap has a reverse flow from the peroneal artery (Fig. 22.34).^{113,116} There are some disadvantages for reverse-flow island flaps regarding venous drainage despite the connections between accompanying veins, and they may

result in venous congestion. Patients with venous insufficiency and increasing age were identified as risk factors for flap complications.¹¹⁷ Other concerns can be the poor cosmetics of the donor site as it has to be grafted for larger flaps and hypoesthesia of the lateral aspect of the foot. Nevertheless, it can provide excellent coverage for heel, ankle and the dorsum of the foot when microsurgery is not feasible.

Turbocharged and supercharged flap

This term was based on the observation of automotive terms by Semple.¹¹⁸ “Supercharging” is using an external power source to boost the engine’s performance. Thus, in addition to its original vascular source, using an unrelated distant vascular source to anastomose to a flap may result in augmentation of either inflow or outflow. An example would be the superior unipedicled transverse rectus abdominis musculocutaneous (TRAM) flap salvaged by an anastomosis of a thoracic or upper extremity vascular source to the contralateral deep or superficial inferior epigastric vessels.^{42,119,120} “Turbocharging” is using the engine exhaust for additional power. Thus, using

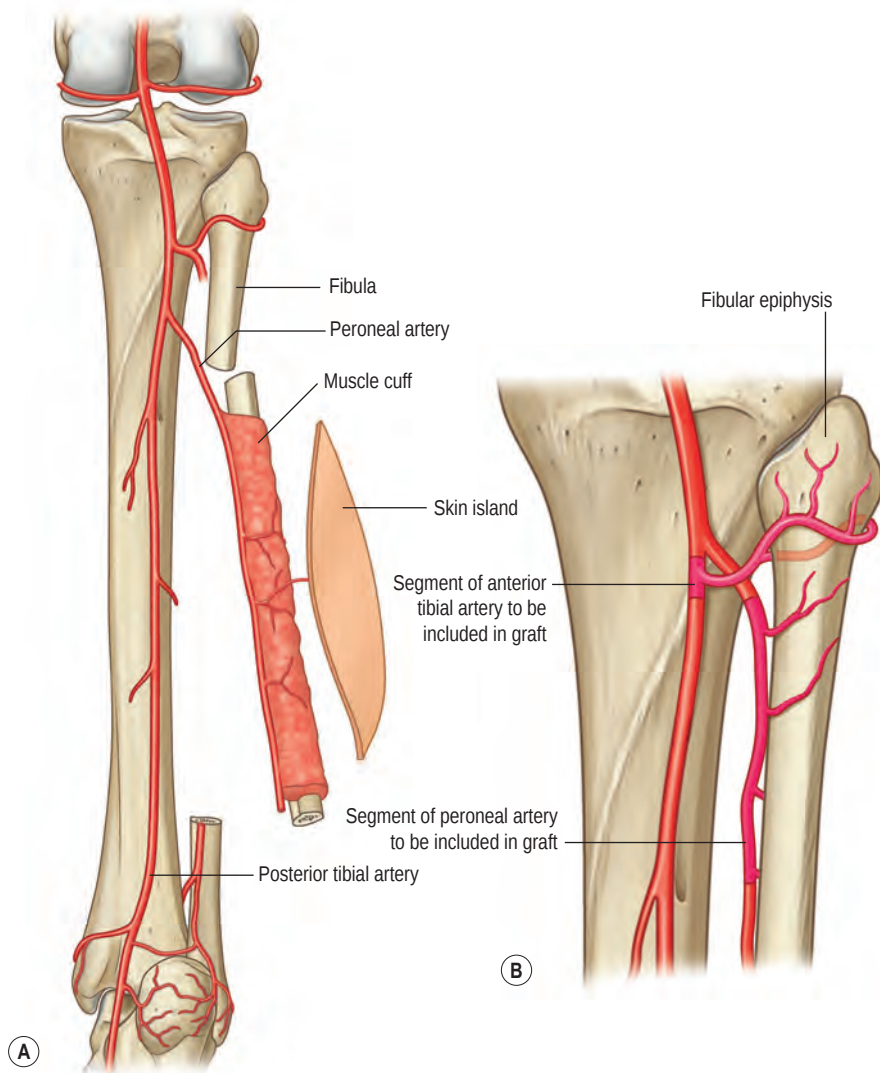


Fig. 22.28 One of the most widely used bones, the fibula, has vascular supply from the peroneal artery, giving rise to multiple arcuate vessels along the fibula and a nutrient vessel in the mid third of the fibula bone (A). The branches of the anterior tibial artery supply the head, neck, and epiphysis and this part of the fibula bone can be used as an osseous flap to reconstruct the defect after proximal humerus resection in a growing child (B).

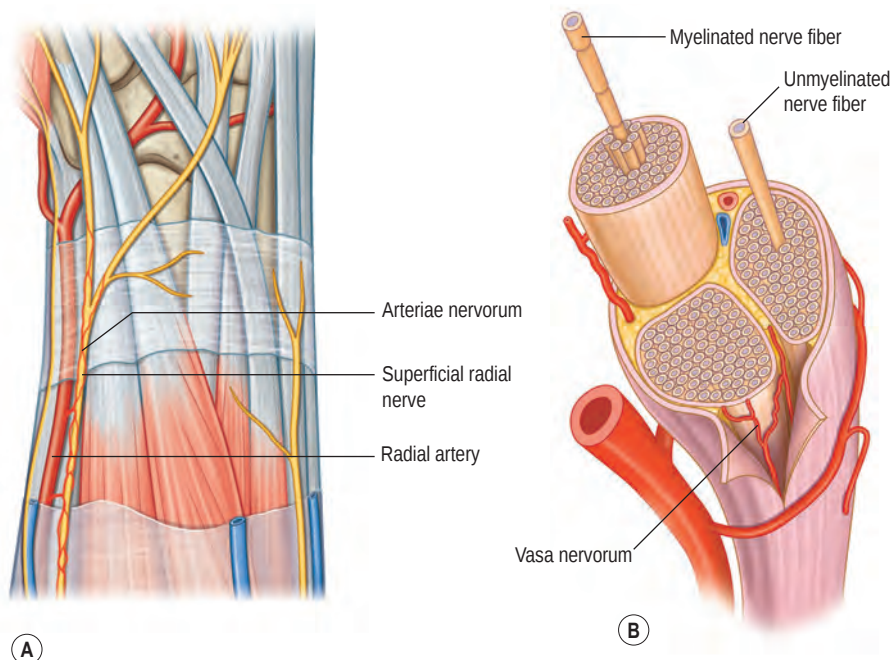


Fig. 22.29 The extrinsic blood supply to the peripheral nerves consists of arteriae nervorum that rise directly from the perforating vessels (A). These small arteriae nervorum enter the nerve and terminate intraneurally. The intrinsic blood supplies are the longitudinally oriented arterioles located on the epineurium, perineurium, and endoneurium (B). Thus, the nerve flap can be harvested from superficially located sensory nerves based on perforating vessels originating from a proximal source vessel.

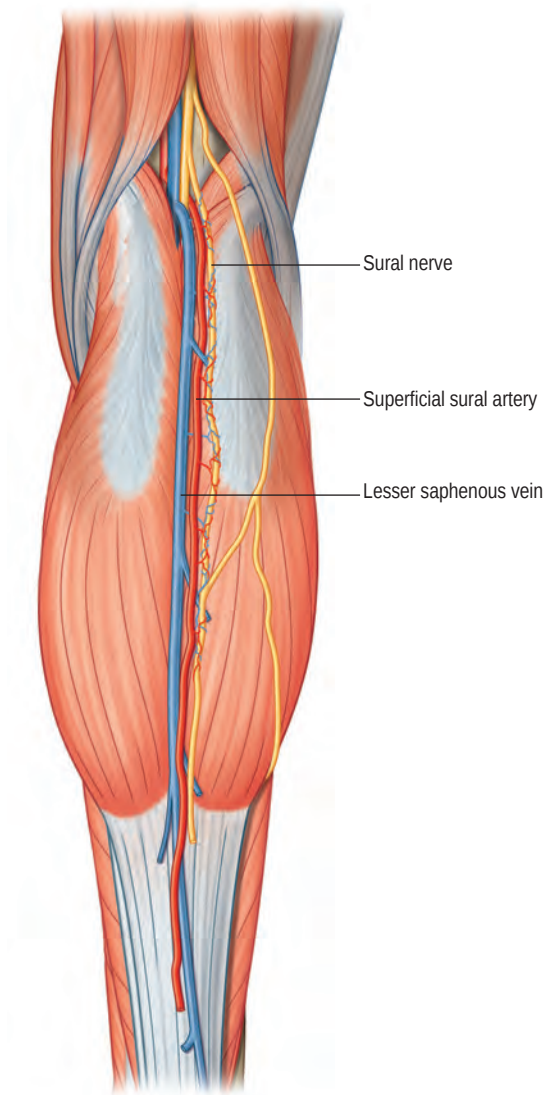


Fig. 22.30 The sural nerve flap, where an arterial supply such as the superficial sural artery, medial or lateral sural artery would be missing and the lesser saphenous vein would be arterialized.

the main vascular source to connect to an additional pedicle from the same flap creates a direct flow to the vascular territory of the connected branch. An example would be directly connecting the ipsilateral and contralateral deep inferior epigastric vessels of a TRAM flap to improve the vascular supply to the whole TRAM flap (Fig. 22.35).^{42,118,121}

Venous flaps (arterialized venous flap)

A venous flap is defined as a composite flap of skin, subcutaneous tissue and other tissues such as nerve, tendon, and bone that uses a subcutaneous vein for the arterial inflow and venous outflow. Nakayama *et al.* first described these flaps in 1981.¹²² Arterialized venous flaps differ from conventional flaps in that the arterial inflow–capillaries–venous outflow is replaced by the arterial inflow–without capillary network–venous outflow. The flap does not require a donor site artery; the flap can be harvested very thinly based on the superficial veins, and can be harvested rapidly. It is widely

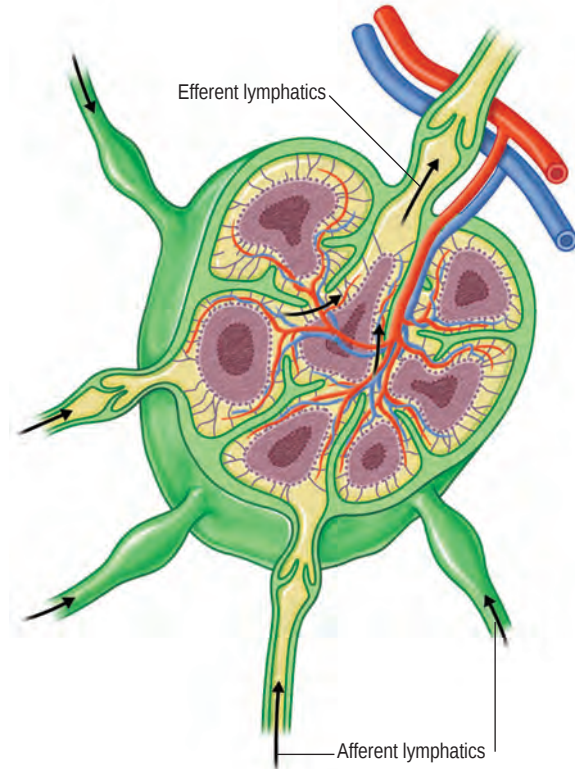


Fig. 22.31 Lymph node vascular supply, based on arterial inflow and venous outflow, should be elevated with the surrounding fat tissue.

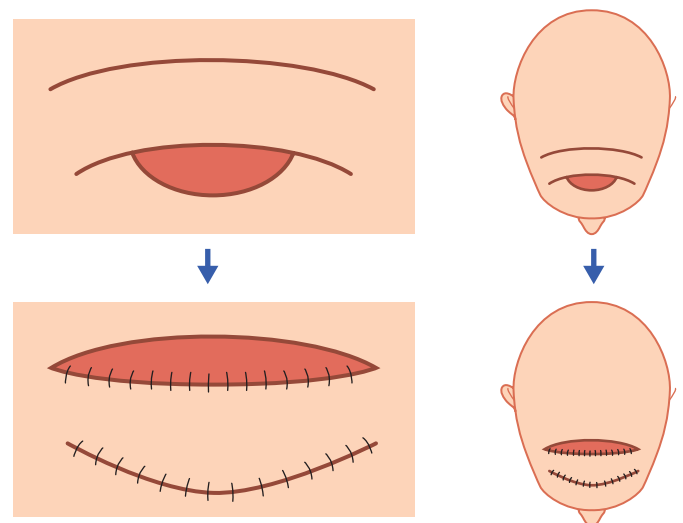


Fig. 22.32 A bipedicle flap is a flap with dual pedicle often used as a random pattern skin flap to cover the defect on the extremity or transabdominal bipedicle flap.

used for soft tissue repair on the hands and fingers when local flaps and other conventional flaps are not readily available.^{123–125} There are considerable controversies on the mechanism of flap survival but three main theories have been postulated: (1) A–V shunting: retrograde flow from the venous system to the arterial system via paralyzed arterial–venous shunts; (2) reverse flow: flow from the venules into the capillaries; (3) capillary bypass: flow through the venous system without entrance into the arterial side until neovascularization.¹²⁶

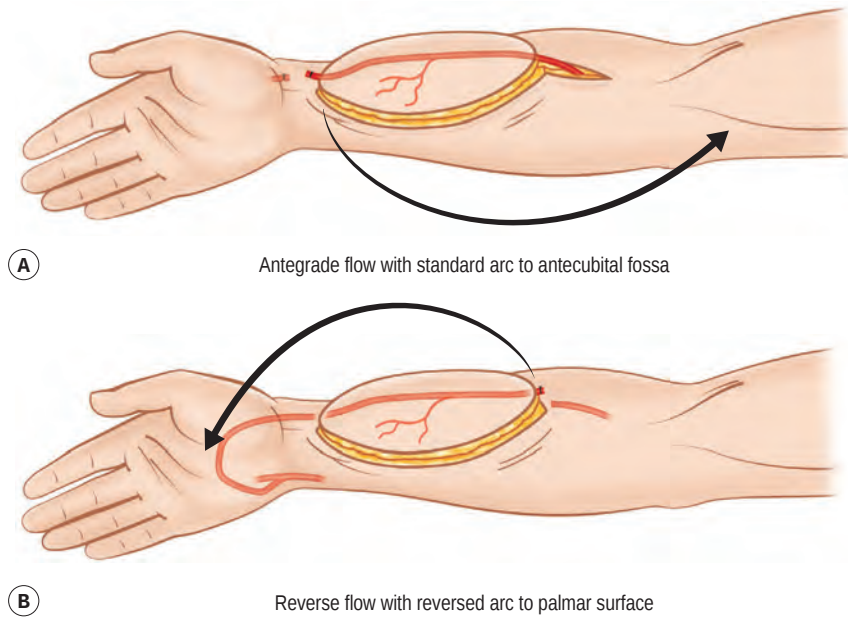


Fig. 22.33 A flap based on the antegrade flow has a major pedicle that flows with the flap (A) but when the same flap has its orthograde pedicle ligated proximally, it becomes a flap based on the distal part of the major pedicle and the flow of the flap becomes reversed (B).

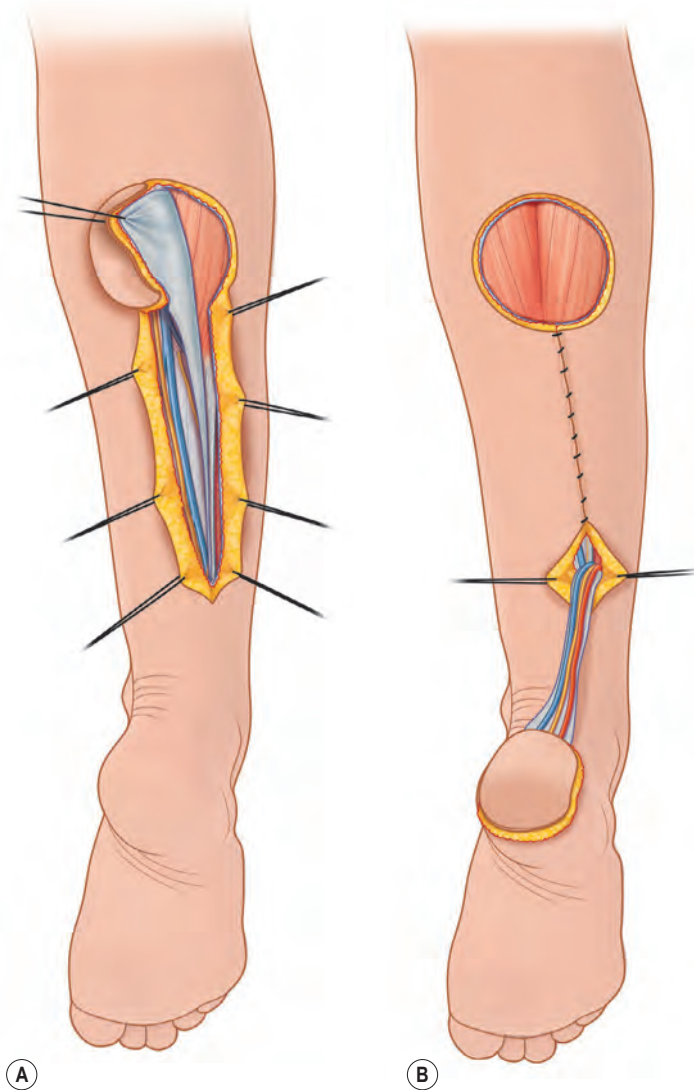


Fig. 22.34 The reverse sural flap is elevated by ligating the sural artery and nerve proximally (A) and distally positioning the flap resulting in a reverse flow from the peroneal artery (B). The arc of rotation allows the flap to reach the heel but skin graft is usually needed to cover the donor site.

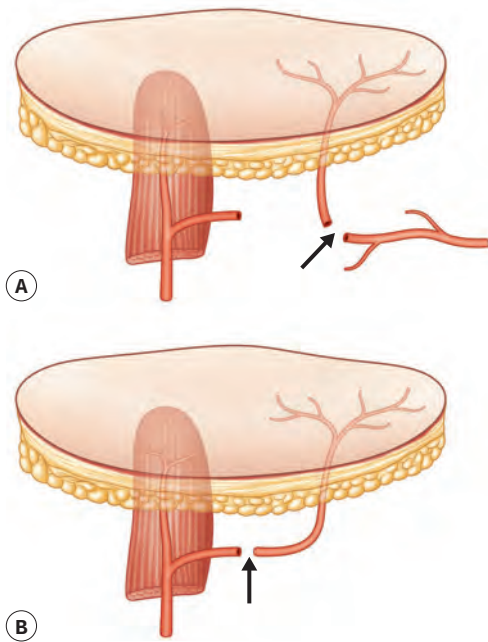


Fig. 22.35 Supercharging is using an external power source to boost the engine's performance (A). Turbocharging is using the engine's exhaust for additional power, like using the same main vascular source to connect to an additional pedicle from the same flap (B).

Based on the earlier classification by Thatte and then by Chen, in 2007, Woo *et al.* refined the classification of arterialized venous flaps used in hand and finger reconstruction into three types.^{125,127,128} Woo's classification is based on the presence of an intravenous valve, the venous network of the donor site, the location, and the number of veins at the recipient site. Type I is a "through-and-along-valve" type which mimics similar blood flow as in a standard vein graft with a straight or Y-shaped pattern. Type II is against-valve, which is arterial inflow against the valve through the afferent vein with a reversed Y- or H-shaped venous network. In type III venous flaps, venous flow drains through efferent veins against intravenous valves (Fig. 22.36).

These flaps have had success in hand reconstruction. The availability of small, thin flaps with defined arterial inflow and venous outflow is limited. Thus, when local flaps are not available, arterialized venous free flaps provide a good solution for successful soft tissue reconstruction (Fig. 22.37).

Flaps based on conditioning

Delay

The delay procedure was naturally developed to overcome the limitations of random pattern flaps. Given the vascular limitations of the random pattern flap, investigators attempted different means by which to maximize the potential area of a flap, which led to the concept of flap delay. Although the delay procedure has been used for several hundred years, it was not until the early 1900s that the concept was recognized. Blair introduced the term "delayed transfer" in 1921.⁸¹ In the 16th century Tagliacozzi delayed his upper arm flaps by making parallel incisions through the skin and subcutaneous tissue overlying the biceps muscle. In 1965, using the pig

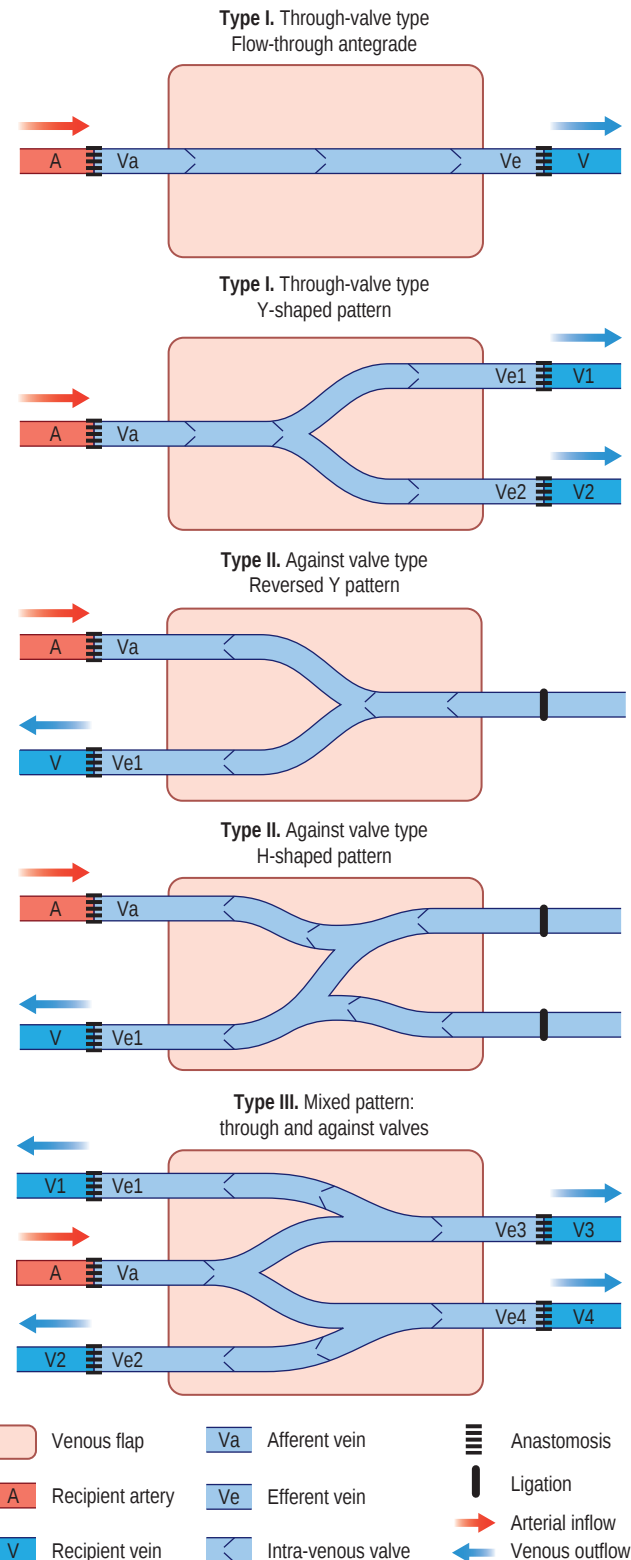
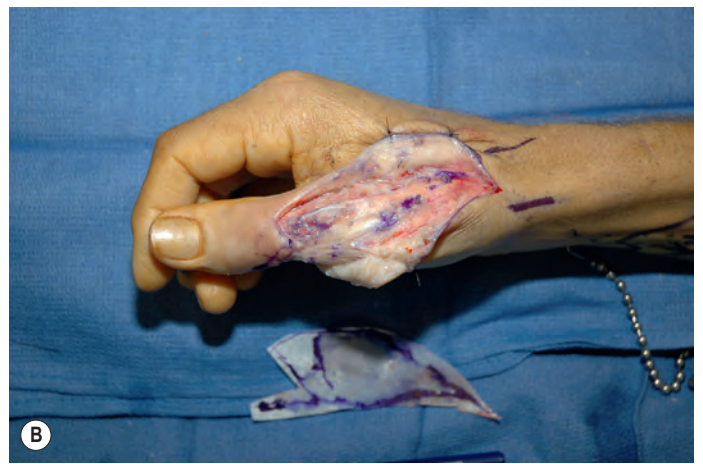


Fig. 22.36 The venous flap classification. Type I is a "through-and-along-valve" type which mimics similar blood flow as in a standard vein graft with a straight or Y-shaped pattern. Type II is against-valve, which is arterial inflow against the valve through the afferent vein with a reversed Y- or H- shaped venous network. In type III venous flaps, venous flow drains through efferent veins against intravenous valves.



https://t.me/Free_Plastic_Reconstruction_Book

Fig. 22.37 (A–H) Venous flap to thumb.

model, Milton investigated the effectiveness of four different methods of delaying a flap. He found that in developing a bipedicle flap, the best form of delay was by making two incisions and undermining the skin between the incisions.³¹ The goal of a delayed flap is to enhance flap circulation, ensuring flap survival after advancement, transposition, or transplantation to a defect site. Flap delay may be used to increase circulation to the muscle or fascia or to enhance vascular connections to the overlying cutaneous territory or adjacent structures to be included during flap elevations (tendon, fascia, and bone). Although delay may be accomplished by biochemical means to improve flap perfusion, currently the most effective method to ensure delay is surgical manipulation of the flap. To date, no pharmacologic method has surpassed the reproducibility and the degree to which surgical delay protects against flap necrosis.⁷⁷ There are two theories that describe the potential mechanism by which the delay phenomenon prevents skin necrosis. The first is that delay acclimatizes the flap to ischemia (tolerance), permitting it to survive with less blood flow than would normally be required. This theory suggests that vascular delay causes adaptive metabolic changes at a cellular level within the tissue.⁹⁶ The second theory is that delay improves vascularity by increasing flow through pre-existing vessels, reorganizing the pattern of blood flow to more ischemic areas.^{103,104} On the basis of experimental data, it appears that both of these mechanisms, either directly or indirectly, contribute to the beneficial effects of surgical delay. Regardless of the underlying mechanisms, most experimental work on surgical delay demonstrates changes at the microcirculatory level.^{129,130}

Surgical flap delay is accomplished in two ways: standard delay, with an incision at the periphery of the cutaneous territory or partial flap elevation; and strategic delay, with division of selected pedicles to the flap to enhance perfusion through the remaining pedicle or pedicles.

The technical aspects of standard surgical delay to enhance circulation are straightforward. The flap cutaneous territory is outlined and incisions are made through all or part of the border of a planned cutaneous territory (Fig. 22.38). Minimal to partial flap undermining is performed. The incisions are then closed. The flap is then elevated after 10–14 days. It has been shown that after 1 week, the blood flow into the area of delay reaches a maximum.¹³¹

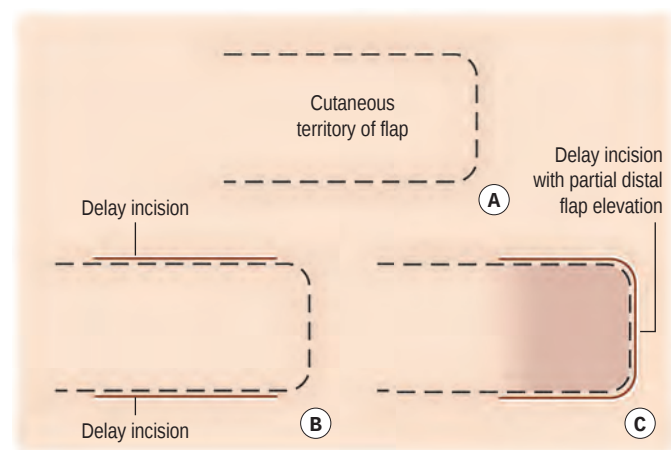


Fig. 22.38 Standard delay flap modification. (A) Cutaneous territory of flap. (B) Delay incision. (C) Delay incision with partial distal flap elevation.

Strategic pedicle delay is accomplished by making incisions at the border of the planned flap cutaneous territory. The dissection is either deep to muscle or fascia, depending on the flap type, to reach pedicles entering the flap territory. These pedicles are divided and the incision is closed. Second-stage flap elevation is performed after a 2-week period. Effectiveness of strategic delay based on ligation of the dominant vascular pedicle was initially demonstrated in the converse model of the gracilis musculocutaneous flap.²² This type of delay is usually advocated in patients with risk factors for flap ischemia (i.e., smoking history, obesity, radiation therapy, abdominal scar). New techniques for strategic delay are designed to minimize incision length and procedure-related morbidity. Endoscopic techniques allow access and division of pedicles with minimal incisions. Interventional radiology techniques may also be used to occlude dominant or secondary pedicles to the flap territory to enhance perfusion to the remaining flap pedicles.

Although important historically, the delay technique is used less frequently because of the development of better techniques, including axial, musculocutaneous, fasciocutaneous, transposition, perforator and microvascular free flaps. As with the random-pattern flap, the limitation of the delayed flap is that a parallel blood supply is not efficient. Flap delay also has disadvantages: a preliminary operation is required; inadvertent injury to the desired pedicle for flap design is possible; and resultant scar tissue at the site of flap delay may impair subsequent manipulation and inset of the flap at the recipient site.

The delay phenomenon may result in part from a sympathetic state that results from cutting the sympathetic innervation to the vasculature and the subsequent vasodilatation. Drugs that block vasoconstriction or those that vasodilate may be of theoretic value. Attempts have been made to stimulate the delay phenomenon pharmacologically by manipulating the autonomic nervous system.¹³² Although pharmacologic delay is of theoretical importance, additional studies need to be done to prove its effectiveness.

Tissue expansion

Skin and soft tissue adjacent to the defect are preferred for the closure of the defect because of the similarity in skin color, texture, and contour. Design of local advancement flaps will frequently allow use of adjacent tissue, particularly if there is skin excess in the donor area. A rotation or advancement flap frequently requires either a back-cut or skin graft at the donor site. The size of the defect or the surrounding zone of injury often prevents the use of adjacent tissue, which is frequently not available for wound closure or composite defect reconstruction. In these circumstances, tissue expansion may allow the use of the desired adjacent tissue for reconstruction. Tissue expansion is an effective method to enlarge the cutaneous territory of superficially located muscle and fascial flaps. Although it is most commonly used to increase the cutaneous flap territory, the principle of tissue expansion may also be applied to all soft tissues, including fascia and peripheral nerve. Neumann is credited with the first modern report of this technique in 1957.¹³³ Radovan further described the use of this technique for breast reconstruction in 1976.¹³⁴

Technically, the tissue expander is inserted under the skin to provide a mechanism for increasing skin dimensions to provide sufficient skin circumference for designing an

advancement or transposition flap. If a fasciocutaneous flap is planned, the expander is placed below the deep fascia. If a musculocutaneous flap is planned, the expander is placed beneath the deep surface of the muscle. The expander should not be placed directly beneath the dominant vascular pedicle at its point of entrance into the flap territory to avoid injury to the pedicle during the expansion process. Although immediate skin expansion is possible, delayed expansion is usually performed prior to flap elevation. During a selected time interval, usually 6 weeks to 3 months, the expander is injected with saline at weekly intervals. Once the desired amount of expansion has been achieved, the expander is removed and the modified flap skin territory is recruited for reconstruction.

Safe tissue expansion depends on surgical judgment regarding its usefulness for a specific problem. The benefits of local surrounding tissues in reconstructive surgery are well recognized; however, this tissue is frequently injured because of its proximity to the traumatic or surgical defect obviating the ability to use this tissue. Failure of tissue expansion is usually attributable to inadequate stability of skin and associated soft tissue during the expansion process. Failure of the expander is signaled by wound dehiscence followed by expander exposure and infection. Unlike failure of flap transposition or transplantation techniques, expander failure is not generally associated with increased wound complexity or donor site problems.^{36,135}

Prelaminated and prefabricated flaps

Flap prelamination, a term coined in 1994, involves surgical manipulation of a flap that requires partial to complete flap elevation and suturing of the flap to form structures at the site of the reconstruction.¹³⁶ This technique may also incorporate new tissues into the flap territory, establishing a multilayered flap. When these structures at the donor site have healed, flap transposition or transplantation is performed. With suture lines or various grafts healed at the time of flap inset, complex reconstructions are theoretically accomplished with less risk of complications at the recipient site. This is commonly done in flaps to be used in head and neck reconstruction. Baudet *et al.* and Pribaz *et al.* have used prelamination techniques on the forearm for nasal and central face reconstruction.^{32,137} Although it is useful, many reconstructive surgeons still prefer to perform secondary procedures after successful initial flap inset rather than flap prelamination at the donor site.

Another form of flap manipulation is termed prefabrication. Prefabrication provides a new dominant vascular pedicle to structures for subsequent transposition or transplantation. A suitable artery and vein are selected and buried in fascia or subcutaneous tissue in the planned flap territory. A large pedicle to an adjacent muscle is frequently used. The pedicle and a small segment of muscle are elevated and inset beneath the proposed flap site. In 6 weeks, the flap based on the new vascular pedicle is elevated and either transposed or transplanted by microsurgery. This technique for prefabrication is not always reliable for establishing a new dominant pedicle to a flap territory. With the numerous options available for safe flap selection, this technique of flap prefabrication is rarely used.¹³⁸

Sensory flap

Specific sensory nerves are identified in the cutaneous territory of many of the flaps available for reconstructive surgery.

All flaps using the skin component may be designed to incorporate the sensory nerve in the flap base. If the cutaneous nerve does not enter the flap base in proximity to the vascular pedicle, it is also possible to divide the sensory nerve during flap elevation and then subsequently coapt the nerve to a suitable sensory nerve at the recipient site.

Muscle flaps with intact motor nerves or with re-anastomosis of the motor nerve to suitable motor or sensory nerves at the recipient site appear to retain protective sensibility, possibly through nerve fibers of proprioception. Maintenance of protective sensation is essential for hands, feet and other weight-bearing areas. Another common area in which sensate flaps are used is the oral cavity and this potentially improves postoperative intraoral function.^{139–141} Harris *et al.* state that reconstruction of weight-bearing areas should provide adequate contour for normal footwear, thick durable skin, protective sensation, and solid anchorage to the deep structures to resist shearing forces.¹⁴² Studies have shown benefits of protective sensation for ankle and heel reconstruction both with rotational flaps and by microvascular tissue transfer.^{110,143,144} Sensory reinnervation for free flaps showed faster sensory recovery and flaps without sensory reinnervation did recover protective sensation but never two-point discrimination.^{144,145}

Functional muscle flaps

Release of the origin or insertion of the muscle transposition flap will result in loss of muscle function. However, many of the muscle flaps may be designed for both coverage and functional muscle transfer. For function to be preserved, the motor nerve must be preserved along with dominant vascular supply, the muscle must be reattached to a new bone or tendon across a joint, and the muscle must exert a direct force on its new point of attachment. Muscles suitable for use as transposition flaps or microvascular composite tissue transplantation, providing both coverage and function, include the latissimus, gluteus maximus (segmental), gracilis, gastrocnemius and serratus muscles. Restoration of the original muscle length-to-width ratio and repair of the motor nerve to a suitable receptor motor nerve at the recipient site are essential for restoration of transplanted muscle function at its new inset site.

Flaps based on conformation

In the era of random pattern flaps, the issues related were regardless of circulation and focused on shapes and the methods to transport flaps to distant regions. Nowadays with complex defects, multiple tissues are used to obtain an ideal reconstruction. The conformation of the flap frequently combines multiple flaps. A compound flap typically consists of multiple tissue components linked together in a manner that allows their simultaneous transfer and consequently more efficient reconstruction.^{39,41,42} Hallock's classification of compound flaps has been simplified to enhance communication and further advance the role of complex flaps, not only microsurgical but local flaps as well (Table 22.13).^{41,42} The compound flap can be partitioned into two major classes according to their primary means of vascularization (Fig. 22.39). First are the "solitary compound flaps" which are composite flaps based on solitary circulation. It is the simplest form of compound flap that contains en bloc multiple

Table 22.13 Classification of compound flaps
Solitary vascularization
Composite flaps
Combined vascularization
Conjoined flaps
perforator-based
branch-based
independent
common
Chimeric flaps
perforator-based
branch-based
sequential
internal

tissue components.²⁹ The components are dependent on each other and must remain intact together supplied by a solitary source.¹⁴⁶ Most of the classic musculocutaneous, septocutaneous, and osteoseptocutaneous flaps can be seen as composite flaps because they basically consist of muscle or fascial plexus connecting with the skin paddle, which is dependent on the perforators originating from muscle or fascia (see Fig. 22.39).

Second is the “combined compound flap” which is a compound flap that has multiple sources and combined vascularization. There are two major subtypes – conjoined flaps and chimeric flaps – primarily differing in physical relationship of their component but retaining an independent blood supply for each component.^{41,42} The “conjoined flaps” are flaps with at least two anatomically distinct territories, each retaining their independent vascular supply but joined by means of some common physical boundary.⁴² Conjoined flaps can be further divided into two subgroups distinguished by the different source of vascularization: perforator based or branch based. The larger caliber and often subfascial or axial branches of the branch-based form may have completely unrelated origins from different angiosomes (the independent type), or these branches may arise from a common source vessel (common type) (Fig. 22.40). The “chimeric flaps” consist of multiple otherwise independent flaps that each have an independent vascular supply, but in turn all pedicles are linked to a larger common source vessel.^{42,146,147} The chimeric flap can be further divided into three subclasses: (1) perforator-based; (2) branch-based; and 3) fabricated. The fabricated component can be

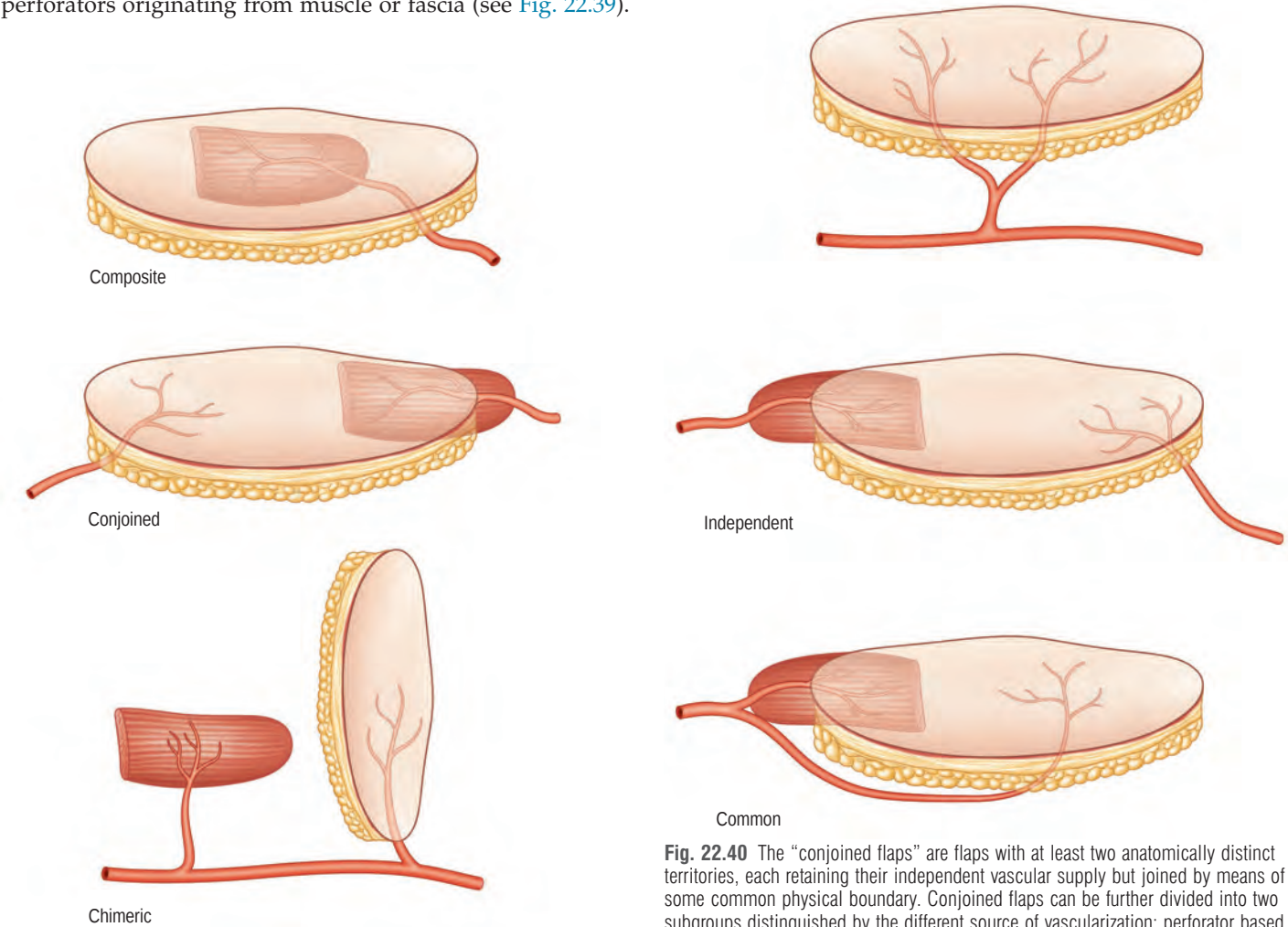


Fig. 22.39 Compound flaps can be subdivided into solitary (composite) or combined types (conjoined and chimeric) based on primary source of vascularization.

Fig. 22.40 The “conjoined flaps” are flaps with at least two anatomically distinct territories, each retaining their independent vascular supply but joined by means of some common physical boundary. Conjoined flaps can be further divided into two subgroups distinguished by the different source of vascularization: perforator based or branch based. The larger caliber and often subfascial or axial branches of the branch-based form may have completely unrelated origins from different angiosomes (the independent type), or these branches may arise from a common source vessel (common type).

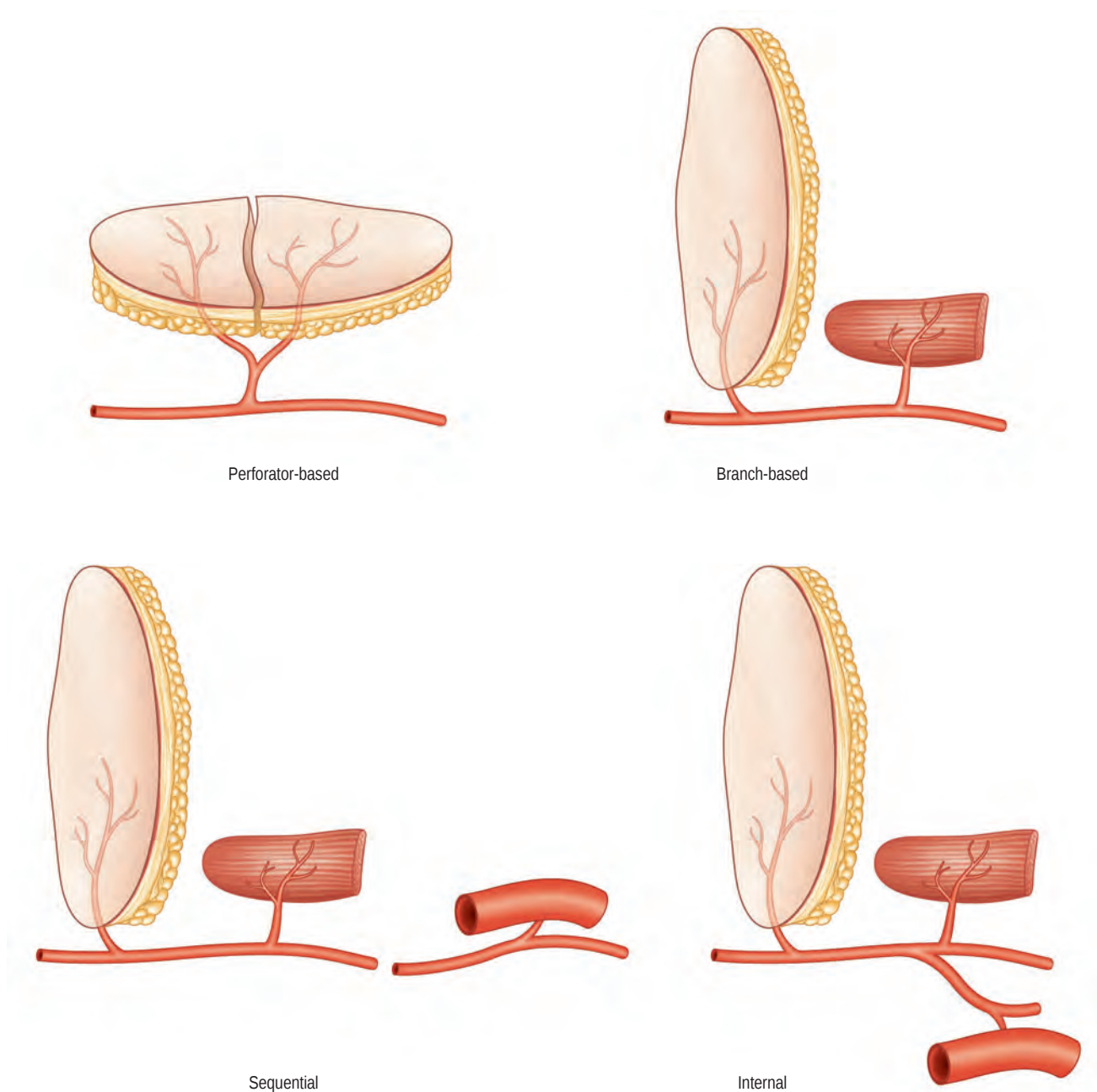


Fig. 22.41 The “chimeric flaps” consist of multiple otherwise independent flaps that each have an independent vascular supply, but in turn all pedicles are linked to a larger common source vessel. It is further divided into three subclasses differentiated by: (1) perforator-based, (2) branch-based, and (3) fabricated. The fabricated component can be attached to the terminus of the source vessel to the combination (sequential type) or to a branch indigenous within the flap (internal type).

attached to the terminus of the source vessel to the combination (sequential type) or to a branch indigenous within the flap (internal type) (Figs. 22.41 & 22.42). Fig. 22.43 shows a patient with tibia and soft tissue defects after trauma being reconstructed using a chimeric fabricated anterolateral thigh (ALT) perforator flap with a small strip of vastus lateralis muscle sequentially combined with contralateral fibula flap. The peroneal vessels are sequentially anastomosed to the descending branch of the lateral femoral circumflex vessel. This approach provides simultaneous transfer of multiple tissues, is able to fill large defects, allows immediate coverage, needs only one recipient vessel site, and enables a

customized approach.⁴² When planning a complex reconstruction, one should ask whether a simpler approach is sufficient and there must be unrivaled advantages to choosing the combined type of compound flap.⁴¹

Flap applications

The reconstructive elevator

Once the cause of defect is determined and relative problems solved or planned for further intervention, soft tissue

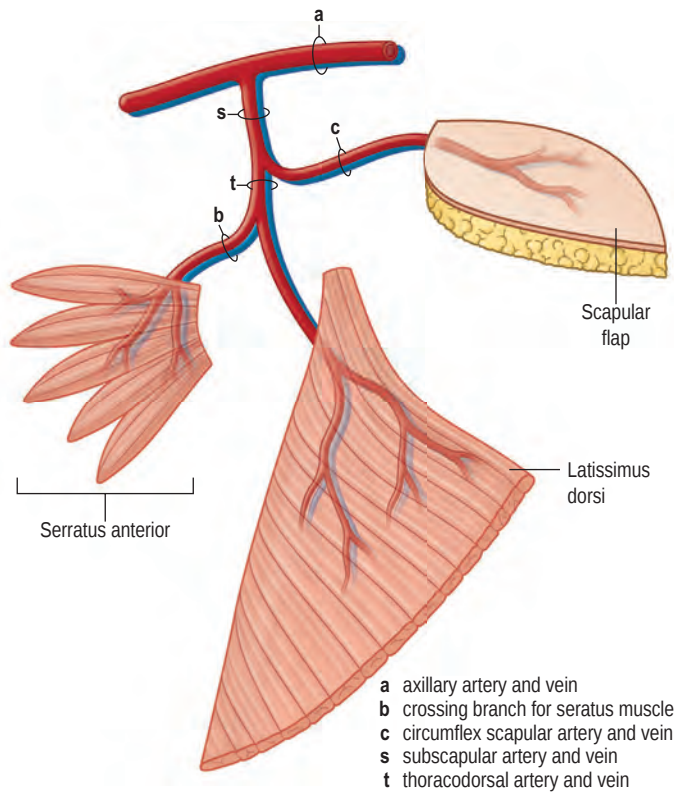


Fig. 22.42 Chimeric flaps from the subscapular artery system.

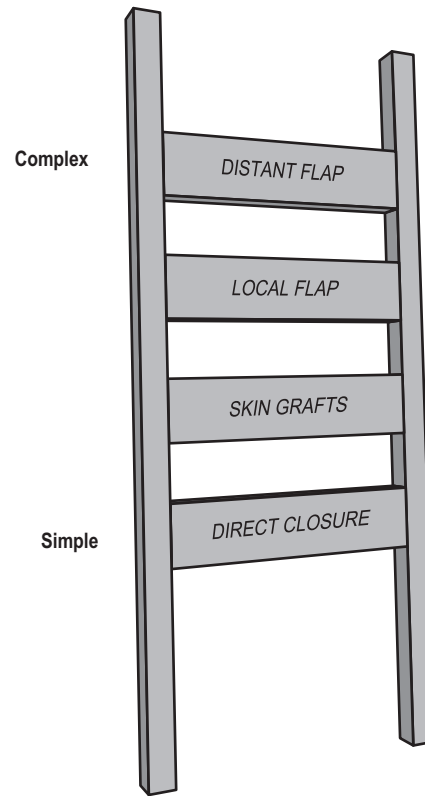


Fig. 22.44 Reconstructive ladder.

coverage is then considered. One must also consider the defect by means of the true defect size compared to the apparent defect. The concept of the reconstructive ladder was proposed to achieve adequate closure of wounds using a step-ladder approach from simple to complex procedures (Fig. 22.44). The reconstructive ladder concept was developed to establish priorities for technique selection based on the complexity of the technique and the defect requirements for safe wound closure. The ladder provides a systematic approach to wound closure, emphasizing selection first of simple and then

complex techniques, depending on local wound requirements and complexity. Direct closure represents the simplest and most straightforward technique. Direct closure may be precluded by the size of the wound or the consequences of wound tension at the closure site resulting in malalignment of adjacent tissues. When this occurs, a more complex closure technique, such as a skin graft that uses distant skin for defect coverage, is required. Although still valued and widely taught, the reconstructive ladder comes from the concept of the wound-closure ladder dating back beyond the era of modern reconstructive surgery.²⁵ A skin graft after mastectomy can still provide coverage but a pedicled TRAM (transverse rectus abdominis muscle) flap will provide superior results in addition to coverage. Now with introduction of DIEP (deep inferior epigastric perforator) flaps, the reconstructive ladder approach seems to show more flaws. In the era of modern reconstructive surgery, one must consider not only adequate closures but form and function. The reconstructive triangle emphasizes the selection of a technique that safely achieves a successful reconstruction and restores form and function (Fig. 22.45). Increased experience has led to the safe use of techniques such as flap transposition, microvascular composite tissue transplantation, and tissue expansion. The surgeon should now consider the reconstructive triangle to select the optimal technique to achieve predetermined reconstructive goals without donor site complications. Other techniques including tissue expansion, skin stretching and vacuum-assisted closure have changed the approach to reconstructive options. A simpler reconstructive option may not necessarily produce optimal results. The “reconstructive elevator” concept proposed by Gottlieb and Krieger suggests the most appropriate floor from which to choose our

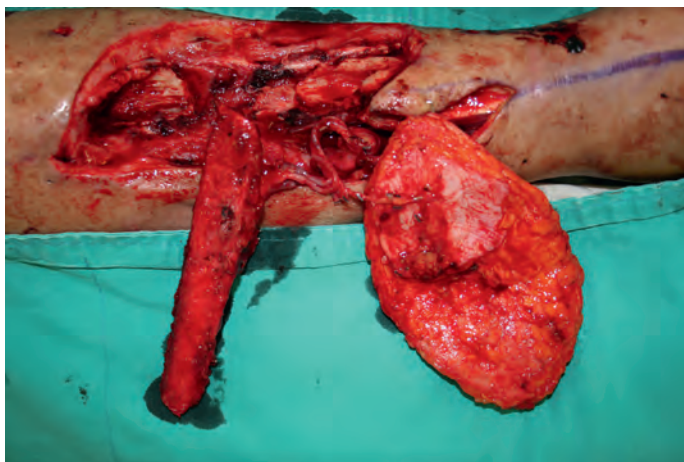


Fig. 22.43 A sequential chimeric flap is used for a patient with tibia and soft tissue defect after trauma. A chimeric fabricated anterolateral thigh (ALT) perforator flap with small strip of vastus lateralis muscle sequentially combined with contralateral fibula flap is shown.

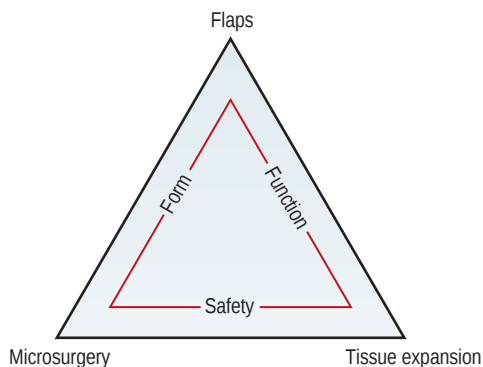


Fig. 22.45 Reconstructive triangle.

reconstruction, based on the specific requirements of the patient, the wound and the circumstances.²⁵ Thus, to provide optimal form and function, we jump up and down the rungs of the ladder. The reconstructive elevator requires creative thought and consideration of multiple variables to achieve the best form and function, rather than a sequential climb up the ladder (Fig. 22.46). This paradigm of thought does not eliminate the concept of the reconstructive ladder but replaces it as a ladder of wound closure and makes its mark in the field where variety of advanced reconstructive procedures and techniques are not readily available. Using the reconstructive elevator, the method of reconstruction should be chosen based on procedures that result in optimal form and function.

The guide for reconstruction using flaps

Flaps, whether pedicled or free, are used to reconstruct defects originating from various causes. However, despite the best efforts, necrosis can occur partially or totally to the flap. The overall survival not only depends on the proper flap selection but preoperative planning, intraoperative techniques and postoperative management involved in reconstruction.

Preoperative planning

Preoperative evaluation is the initial step for all reconstruction. One must think about the final outcome and the

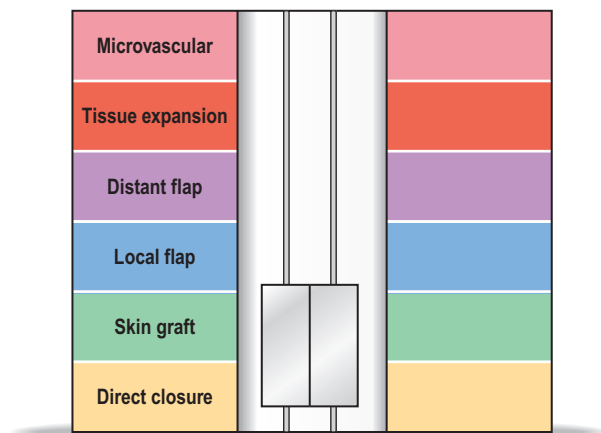


Fig. 22.46 The “reconstructive elevator” concept suggests the most appropriate floor from which to choose our reconstruction, based on the specific requirements of the patient, the wound and the circumstances.

surrounding factors during the preoperative planning. Surrounding factors may include whether the patient will have psychological support, be irradiated, undergo any secondary procedures, need prosthesis, or be ambulant, among others. Once a rough plan has been postulated, the first critical step is for the surgeon to educate the patient about the procedure and the possible outcome, obtaining an informed consent.¹⁴⁸

The recipient site should be evaluated for the vertical and horizontal aspect of the defect. The vertical aspect may include subcutaneous tissues like bone, muscle, tendon, nerve, major vessels, and other deep tissues. The horizontal aspect should address the skin paddle size and the thickness of the skin flap. Added function such as functional muscle or sensate flaps should be planned based on the need of the recipient. Wound analysis includes assessment of the defect in terms of location, size and physical components. When the defect involves a significant percentage of the body surface area (e.g., burns or giant hairy nevus), the reconstructive options may be limited to skin grafts for acute coverage (e.g., burns) or sequential tissue expansion for elective reconstruction (e.g., giant hairy nevus). Complex reconstruction may need to combine various flaps as conjoined or chimeric flaps to achieve ideal reconstruction. Each component affects function and form at the defect site. Selection of a reconstructive option is based on the feasibility and relative importance of replacing each component of the defect. Preoperative planning allows designing and selecting the ideal vascular system to combine various tissues.

Systemic factors should also be considered prior to reconstruction. Obesity, smoking, hypertension, immunosuppression, heart failure, diabetes, hypercoagulability, peripheral vascular disease, chronic renal insufficiency, and others are known to be related to higher complications of donor and recipient sites including flap failure.^{149–157} However, as the development of microsurgical instruments and technique continues, well-known risk factors seem less significant in outcome of flap survival. Nevertheless, these systemic factors should be controlled to minimize not only flap-related complications but also donor site complications.^{151,153,158}

Imaging using CT (computed tomography) scans, angiograms, or MR (magnetic resonance) angiograms help to identify the vasculature of the recipient and donor site. The use of CT angiography may obtain vascular information of the recipient region without the risk of complications from arterial puncture of the groin and can also provide vascular information of the donor flap facilitating the planning and the surgical procedure.^{159,160} Fig. 22.47 shows that the descending branch of the lateral femoral circumflex artery is the collateral vessel responsible for flow to the distal leg and one should not harvest the anterolateral thigh flap based on this major collateral as it may hinder the flow to the leg. In association with prior injuries to the lower extremity, the routine preoperative use of angiogram is controversial but selectively recommended in patients who have loss of one or more peripheral pulses, a neurologic deficit secondary to the injury, or a compound fracture of the extremity that has undergone reduction and either external or internal fixation.¹⁶¹ Prior trauma or incisions may also end in damage of the vascular pedicle of the flap and thus warrant preoperative imaging to confirm the pedicle status. The use of preoperative imaging has now expanded to gather information on the pedicle of the perforator flap. It can show the emerging perforator of the superior



Fig. 22.47 The angiogram shows that the descending branches of the lateral femoral circumflex artery are the collateral vessels responsible for flow to the distal leg. This information can be vital in maintaining the flow to the distal leg and ALT flaps should not be elevated.

gluteal artery piercing the deep fascia reaching the skin. This image allows us to visualize the perforators and to select the best perforator for this flap. The CT angiogram gives information such as the caliber of the pedicle, the intramuscular course of the pedicle, location of the corresponding flap, and the subcutaneous branching from the pedicle. This information allows for more detailed preoperative planning regarding the flap. The CT angiogram remains the gold standard for preoperative imaging.¹⁶²

Hand-held Dopplers allow us to simply and quickly gather information about the perforator and the main axial vessels. However, it may lack detailed information such as the course of the perforator and the actual positive finding may not correlate clinically. Nevertheless, hand-held Dopplers remain the first-line tool to gather information regarding the pedicle of the flap. The color Doppler imaging provides better information and helps the surgeon to identify the presence of the vessels, the direction of the flow, whether the flow pattern is venous or arterial, and the flow velocity.¹⁶³

For local flaps, flap loss may result when the defect is located beyond the standard arc of rotation causing excessive tension on the vascular pedicle. Defect size beyond the vascular territory of the flap pedicle may result in either an inappropriate increase in flap dimensions or excessive flap tension at the inset site. Selection of a flap with a pedicle location in the zone of injury or use in patients with pre-existing vascular compromise may result in failure. Flap modifications, including segmental and distally based designs, are also subject to vascular compromise and potential loss. Thus, flap success is determined preoperatively based on anatomic design and on assessment of the specific reconstructive requirements.

Flap selection should be based on the defect's need for form and function. Safe and reliable muscle or musculocutaneous and fascial or fasciocutaneous flaps and perforator flaps have been described for use in all areas of the body. When design is properly based on the precise vascular territory of their vascular pedicles, the majority of flaps survive transposition to a defect. The technique selected for defect closure or reconstruction should restore normal shape or contour. Although initial experience with the musculocutaneous flaps resulted in safe wound closure, the excessive bulk was often unsightly. Frequently, a muscle flap with a skin graft provided a superior restoration of form at the recipient site. With the identification of muscle and fascial units suitable for design either as a standard transposition or microvascular composite tissue transplantation, the surgeon may select the flap best suited for defect closure. When a skin island is required, the surgeon may select a flap with a thin layer of overlying subcutaneous tissue (i.e., radial forearm flap or a perforator flap) or may plan secondary flap revision by direct excision or suction-assisted lipectomy to improve flap contour in thicker flaps. The availability of numerous flap donor sites allows selection of a technique for either standard transposition or microvascular composite/compound tissue transplantation that best restores form for reconstruction. Specialized functions at the site of reconstruction include hair growth, sensibility, skeletal support (bone), and motion (animation). Techniques of reconstruction must consider these specialized requirements. Although function restoration may require staged procedures, especially for a composite defect, it is often possible to restore all functional requirements with a single procedure. After evaluating the character of the defect, [Table 22.2](#) may guide the selection process of the flap based on circulation, composition, contiguity, construction, conditioning and conformation. The final flap design is usually delayed until dimensions of the defect is confirmed. One should think of the true defect compared to the apparent defect. An ideal reconstruction would replace defect with like tissue or with tissue that will best give the form and function.

Donor site morbidity should also be considered when selecting a flap. When possible, the donor site should be closed directly to preserve form. Use of a flap that requires a skin graft for donor site closure is justified when the flap harvested is clearly superior to alternate flaps for the defect. If it is possible to stage the flap elevation with preliminary insertion of a tissue expander, an increase in both the cutaneous flap dimensions for defect closure and the adjacent skin territory for donor site direct closure may be accomplished. Although the ultimate form at the flap recipient site remains the primary basis for flap selection, deformity due to loss of form at the donor site should be avoided when possible. Thus, reconstructive balance is achieved with selection of a tissue source to restore the defect or deformity while form and function are preserved at the donor site. In an effort to minimize donor site morbidity, many surgeons have evaluated the utility of endoscopic harvest of muscle flaps. Minimally invasive techniques for harvest of several muscles have been described. These include the latissimus dorsi, rectus abdominis, gracilis, rectus femoris, external oblique, and gastrocnemius muscles. In addition to the endoscopic harvest of muscles, laparoscopic techniques are frequently used to harvest the omentum. This has been a significant advance as the benefits include decreased scarring, less postoperative

pain and theoretically less donor site morbidity.^{164–166} Skin or perforator flaps have evolved to harvest flaps from less conspicuous sites. Although many factors are involved when choosing a perforator flap, DIEP (deep inferior epigastric perforator), SGAP (superior gluteal artery perforator), SCIP (superficial circumflex iliac artery perforator), and TDAP (thoracodorsal artery perforator) flaps are well hidden in regular clothing and have minimal donor site morbidity.

Finally, for the preoperative planning, the surgeon should always think of a plan B flap just in case plan A does not go as ideally planned. This allows preoperative visual practice, reduction of surgical time, minimizing unwanted variables, and to maintain the high spirit of motivation.^{167,168}

Intraoperative techniques

When possible the patient is positioned to allow visualization of both donor and recipient sites. This allows a two-team approach and does not need additional surgical time to change the patient's position during operation. The patient in Fig. 22.48 shows a defect on the posterior aspect of the heel pad with chronic osteomyelitis. After complete debridement, a superior gluteal artery perforator flap was used to reconstruct the heel pad without changing the patient position during surgery.¹⁶⁹ For surgeries with an expected long operating time, careful padding of potential pressure sites to avoid injury to normal structures, active warming to minimize hypothermia (which may decrease peripheral blood flow), deep vein thrombosis prophylaxis, and an intensive glucose control for diabetes are needed to ensure a positive outcome.¹⁴⁸

The recipient site must be completely ready prior to flap application. For cancer, adequate resection margins must be obtained and wounds must achieve a clean field through debridement. The design of the flap is of paramount importance. The final design of a flap intended for standard transposition, staged expansion, or microvascular transplantation should be based on the actual defect size. The original design of the flap has an impact on future procedures if the defect should recur or require further revisions. In general, flap design is delayed until adequate wound debridement or tumor resection is accomplished. If simultaneous flap elevation and resection are performed, the flap design should allow for the maximal defect size. If tissue expansion is used, the expander advancement or transposition flap should be elevated and advanced to the potential defect site before the resection is performed. Repeat expansion will be necessary if adequate tissue is not available to cover the defect created at the resection site. A careful assessment should be made of the extent of debridement required to remove nonviable structures subject to bacterial invasion and impaired vascularity. Inability to accurately predict the amount of debridement required may necessitate sequential wound debridement with subsequent wound observation and bacterial culture of the wound. When regional vascular insufficiency involving the wound site is observed, preliminary or simultaneous vascular procedures may be required in conjunction with wound debridement and coverage. The continuing debate on which flap composition is better for chronic osteomyelitis remains, but growing reports have shown that with adequate debridement, flaps – whether they be primarily muscular or skin component – can be equally effective.^{170–174} Furthermore, the skin/fasciocutaneous flaps better allow for

staged reconstructions, are easy to elevate and are less scarred and fibrotic when compared to muscle flaps. They also provide a thin flap which leads to very good aesthetic results.¹⁷⁴

Flap elevation requires precise knowledge of flap anatomy. Random pattern flaps are still used commonly in smaller wounds but as the flap gets larger, identification of the pedicle and angiosome increases the chance for success. In the case of free flaps, the recipient vessels need to be ready and patency confirmed prior to microsurgery.

When inseting the flap, tension must be avoided especially around the vascular pedicle. Postoperative swelling should be taken into account as swelling will increase tension. Meticulous coagulation of the flap as well as the recipient bed is crucial to minimize hematoma after surgery. A closed suction drain system is generally used at both the donor and recipient closure sites. One must be careful not to place the drain near the pedicle as the negative pressure of the drain may compress the pedicle.¹⁷⁵ Drains are not removed until the patient is mobilized since the resultant motion may temporarily increase the risk of seroma formation. Drains in proximity to a tissue expander or prosthetic implants are a potential source of infection and are removed as quickly as possible. When seroma drainage decreases to 20 mL in a 24-hour period, the closed drainage system is removed. When possible, drainage systems are removed by postoperative day 10 to avoid potential wound contamination through the drain exit site.

Postoperative management

Postoperative flap management is of equal importance to the success of a reconstruction. The maintenance of proper positioning, temporary immobilization, and proper dressing of the wound are critical.

Pressure on the flap base is to be avoided during the postoperative period. When possible, the area of the flap inset is elevated as in head and neck and extremity reconstruction. If the area of the flap lacks protective sensation, the site of reconstruction is placed in a nondependent position. Use of an air-fluidized bed is recommended to avoid pressure on dependent areas in patients with spinal cord injury.

Constricting bandages are avoided, particularly in the area of the flap base where pressure on the flap pedicle may compromise flap circulation. The flap is observed for potential circulatory problems during the initial postoperative period. Those patients undergoing head and neck reconstruction with microvascular tissue transfer should have strict orders to have nothing placed circumferentially around the head or neck. Nasal cannulas, oxygen masks, eye glasses, and tracheostomy collars should be avoided due to the risk of pedicle compression.

Excessive motion in the area of the flap inset is to be avoided by padding of areas adjacent to the flap inset site. In extremity reconstruction, the use of a plaster splint to immobilize the joint proximal and distal to the flap inset site is recommended. Circular casts are avoided because of the risk of pressure associated with postoperative edema and difficulty in observing flap circulation.

Perioperative antibiotics are recommended when flaps are inset at the site of contaminated defects. If an expander or permanent implant insertion site has a history of prior infection, perioperative antibiotics are also recommended. Cultures of the wound site will determine the necessity for



Fig. 22.48 Using an available flap without changing position allows for a safe and faster surgery. The patient shows a defect on the posterior aspect of the heel pad after resection of malignant melanoma (A). A flap is designed and elevated based on the superior gluteal artery along with the superficial nerve (B). Follow-up shows good contour of the heel and the donor site (C,D).

postoperative antibiotic therapy. Continued use of postoperative antibiotic therapy should be based on wound cultures and selection of culture-specific antibiotic agents.¹⁷⁶

Prolonged bed rest is avoided when possible following reconstructive surgery. With the exception of those undergoing reconstruction of the perineum and lower extremity, most patients are ambulatory after the first postoperative day. Elevation and immobilization of upper and lower extremities are generally recommended for 10 days followed by nonweight

bearing for up to 6 weeks. Weight bearing at the site of flap inset for pressure sore coverage is avoided for 4–6 weeks. Range of motion exercises at the donor site are encouraged when wound healing is complete, usually by postoperative day 7–10, to avoid joint stiffness and muscle weakness.

If the patient has difficulty regaining function at either the donor or recipient sites, a physical therapy program is recommended. Pain management for patients treated for complex defects may require consultation with a pain specialty clinic

and psychiatrist. Occupational therapy is indicated for patients unable to return to their jobs. A multi-specialty approach to patients who have undergone cancer treatment is essential to provide tumor surveillance and adjuvant therapy when indicated. Patients at risk for wound recurrence, particularly following closure of a pressure sore, and patients with spinal cord injury require instruction in avoidance of pressure and shear forces at the site of flap reconstruction and assistance in obtaining devices (i.e., wheelchair with appropriate padding) to avoid future skin injury.

Although there is no concrete evidence for the use of postoperative antithrombotic therapy, use of anticoagulation is still practiced by many surgeons and is usually of concern in microvascular tissue transplantation.²⁵ Common postoperative regimens include daily aspirin, heparin or dextran. Aspirin inactivates platelets by blocking cyclo-oxygenase. Heparin is an antithrombin III inhibitor. Dextran decreases platelet adhesiveness, inhibits platelet aggregation and decreases the blood viscosity. The use of these medications varies among surgeons.

Postoperative monitoring of a flap is a critical component in patient care after reconstruction. Many techniques have been developed to monitor flaps and have primarily focused on those flaps transferred microsurgically. These monitoring methods assess the patency of the small vessel microanastomosis. The goal is to discover any problem with the anastomosis early enough to salvage the flap. Musculocutaneous or perforator flaps, which have not been divided from their vascular pedicle, are generally monitored with clinical observation. Clinical observation generally involves assessment of skin color, tissue turgor, temperature, capillary refill, and pinprick. The ideal monitoring measure should be reliable, reproducible, sensitive, cost-effective, user-friendly, and continuous.¹⁴⁸ Adjunctive measures such as laser flowmeter, implantable Doppler, oxygen partial pressure probe, transcutaneous oxygen tension, Duplex scans, and hand-held Doppler can be used to assist the subjective monitoring of the flap.

Selection of specific flaps

Muscle and musculocutaneous flaps

After the decision has been made to use a muscle or musculocutaneous flap, the specific muscle must be chosen. General guidelines used to assist in the selection of a muscle include the following:

1. Ideally, the muscle should be adjacent to the defect.
2. The muscle should be of sufficient size and bulk to cover the defect. The final design of the flap should occur only after the defect is completely defined. When tumor exposure or wound debridement is required, the defect is often much larger and deeper than initially anticipated. By final design of the flap after debridement, costly errors in inadequate coverage can be avoided. If the defect is unstable or the margins are unclear (tumor pathology not available), wound packing or temporary skin graft coverage is warranted. One must also take into consideration that a significant amount of atrophy occurs if the origin, insertion, or motor nerve of the muscle is disrupted.
3. The muscle should be expendable. There are often synergistic muscles that can compensate for the loss of

the selected muscle so that the donor site is not impaired. However, if no synergistic muscle groups are available, either techniques to preserve donor muscle function (e.g., muscle splitting) should be employed or a different muscle chosen.

4. The status of the vascular pedicle that will sustain the proposed flap must be known preoperatively. Selective arteriography must be considered if there is a history of previous surgery in proximity to the vascular pedicle of the proposed muscle flap or if muscle paralysis is noted on physical examination. Earlier division of the motor nerve may also include ligation of the vascular pedicle. Examples of clinical situations when arteriography is particularly useful include the evaluation of the sural artery (gastrocnemius) after knee surgery, of the transverse cervical artery (trapezius) after neck and shoulder surgery, and of the thoracodorsal artery (latissimus dorsi) after axillary surgery.¹⁴⁹
5. The donor defect must be carefully considered. Some patients do not accept the use of a skin graft at the donor site, and certain muscles are more likely than others to require grafts for closure. Likewise, some patients prefer one scar site to another (e.g., the abdominal scar of the TRAM flap versus the back scar of the latissimus dorsi flap in breast reconstruction).
6. The cutaneous territory of the proposed flap must be of sufficient size and of acceptable texture. The harvested skin should be an acceptable match to the recipient site (e.g., not hair-bearing).
7. If restoration of sensation or motor function is necessary a select number of muscle, musculocutaneous and fasciocutaneous flaps are available. Common examples of muscles which provide sensation or restore function include the serratus muscle, rectus abdominis, and latissimus dorsi.¹⁷⁷⁻¹⁸¹
8. Osteomusculocutaneous flaps are available for defects in need of vascularized bone in addition to soft tissue. Examples include the trapezius flap with vascularized clavicle and scapular spine,^{150,182} pectoralis major flap with vascularized rib,^{183,184} iliac osteomusculocutaneous flap based on the ascending and transverse branches of the lateral circumflex femoral system^{167,185} and the latissimus dorsi-scapular osteomusculocutaneous flap.^{163,186}
9. The operation should be technically straightforward.

Fascia, fasciocutaneous and perforator flaps

General guidelines for choosing a specific fascia, fasciocutaneous flap and basing perforator flaps on known perforators are similar to those for muscle and musculocutaneous flaps, with a few exceptions.

The fascia, fasciocutaneous or the perforator flap must be in the proximity of the defect if a rotational/propeller flap is planned. The planned flap must be of sufficient size and bulk to reconstruct the defect. Fascia, fasciocutaneous and perforator flaps are ideal for areas that do not require bulk. The vascular supply of the area must be assessed preoperatively. If a fasciocutaneous or a perforator flap is planned, the perforating vessels should be assessed with a Doppler probe preoperatively so that the skin island can be designed. The

presence or absence of sufficient perforating vessels determines whether a specific fasciocutaneous or perforator flap can be used. Following the angiosome principle, only one adjacent territory should be included to ensure adequate vascularization of the entire flap.³³ For perforator flaps, after identifying the main perforator, other minor perforators are eventually transected at the level of the deep fascia. However, if minor pedicles are dissected together with the source vessel, the perforator flap will have a better circulation. The donor defect should be considered. These can generally be closed primarily (fascial flap) but may require skin graft if the skin island is large. Restoration of sensation with a fasciocutaneous or perforator flap is possible.

Perforator flap (free-style)

In contrast to elevating a flap on a previously identified perforator, the skin island can be selected first and the appropriate perforator located on the flap can be selected in a sequence. This is the core of the free-style approach and allows efficient handling of unexpected events which occur during flap harvest or in cases with anatomical variations.^{187,188} A specific donor or source artery does not limit the surgeon. After the location and dimension of the flap are determined and specific donor site is selected, the search for the proper perforator is performed. Although this approach provides maximum liberty for flap selection, a learning curve is required to be comfortable with this approach.¹⁸⁹

Regional application of flaps

Head and neck reconstruction

Regional flaps:

1. Temporalis
2. Sternocleidomastoid
3. Platysma.

Distant flaps:

1. Pectoralis major
2. Trapezius
3. Latissimus dorsi.

Perforator flaps

1. Facial artery perforator
2. Submental artery perforator.

Radical cancer surgery or traumatic injury can produce massive defects in the head and neck. Whereas many simple defects can be adequately treated with direct closure, local scalp flaps or skin grafts, the more complicated defect requires a larger reconstruction. The muscle, musculocutaneous and fasciocutaneous flaps play a major role in these reconstructions. Historically, large surgical defects of the head and neck were managed with staged reconstruction. Currently, the most common reconstruction involves microvascular tissue transfer.

The primary applications of the muscle or musculocutaneous flap in head and neck reconstruction include provision of tissue bulk for a significant defect (e.g., after hemimandibulectomy); protective coverage of vital structures (e.g., the carotid artery); provision of skin for intraoral lining and

coverage; and provision of skin for skull, facial, and neck defects.

The local muscle and musculocutaneous flaps for head and neck reconstruction include the temporalis, sternocleidomastoid, and platysma flaps.

The temporalis muscle is a type III, fan-shaped, bipenniform muscle. Transposition of the muscle as a turnover flap is especially useful for coverage of the orbit, superior maxilla, and ear.

The sternocleidomastoid is a type II muscle, first described in head and neck reconstruction by Owens in 1955.¹⁹⁰ This flap has historically been used for intraoral and pharyngeal reconstruction. Other uses have included augmentation of soft tissue defects of the upper neck and jaw, protective coverage of major vessels, and closure of pharyngocutaneous fistulas.^{191–193} However, of all the musculocutaneous flaps used for head and neck reconstruction, the sternocleidomastoid is considered the least reliable.^{20,193}

The platysma is a type II, thin, broad, sheet-like muscle extending over the entire anterior and lateral aspects of the neck. The use of the platysma as a musculocutaneous flap was first described in 1887 by Gersuny, who employed it in reconstructing a full-thickness defect of the cheek.¹⁹⁴ The platysma has been used for intraoral, lip, lower midface, and anterior neck reconstruction. Because of the thinness of the platysma muscle, the reconstructive surgeon must be particularly careful to avoid disrupting the muscle fibers during the dissection and placing undue tension on the vascular pedicle after transposition of the flap.

The distant muscle and musculocutaneous flaps used in head and neck reconstruction include the pectoralis major, trapezius, and latissimus dorsi flaps.

The pectoralis major is a type V, large, broad muscle. Its use as a musculocutaneous flap was first described in 1968 by Hueston and McConchie as part of a compound deltopectoral flap.¹⁹⁵ In 1977, Brown *et al.* described the use of the pectoralis major as a flap in mediastinal coverage.¹⁸ In 1979, Ariyan introduced the pectoralis major musculocutaneous flap for head and neck reconstruction (Figs. 22.49 & 22.50).²⁰ During the ensuing years, the pectoralis major musculocutaneous flap proved more valuable than the deltopectoral flap and supplanted it as the primary flap (other than microvascular tissue transplantation) in head and neck reconstruction.

The common applications of the pectoralis major musculocutaneous flap in head and neck reconstruction include the following: external resurfacing of the skin of the face and neck; intraoral and pharyngeal lining; carrying vascularized rib and skin in mandibular reconstruction; and reconstruction of the esophagus.^{196–200} Historically, the pectoralis major musculocutaneous flap has been one of the most versatile flaps used in head and neck reconstruction.

The trapezius, a type II muscle, is less widely used than the pectoralis major muscle, yet its superior location and wide anterior arc of rotation make it a valuable musculocutaneous flap.^{14,22} Modifications in design have enabled the trapezius muscle to be used as distinctly different upper and lower musculocutaneous flaps.²⁰¹ The various clinical applications of the trapezius flap have included lower facial reconstruction, especially the ear and parotid regions; lateral upper face and scalp (occipital and temporal) repair;²⁰² anterior and posterior neck reconstruction;²⁰³ orbital reconstruction with the use of an extended flap;^{204,205} and pharyngoesophageal

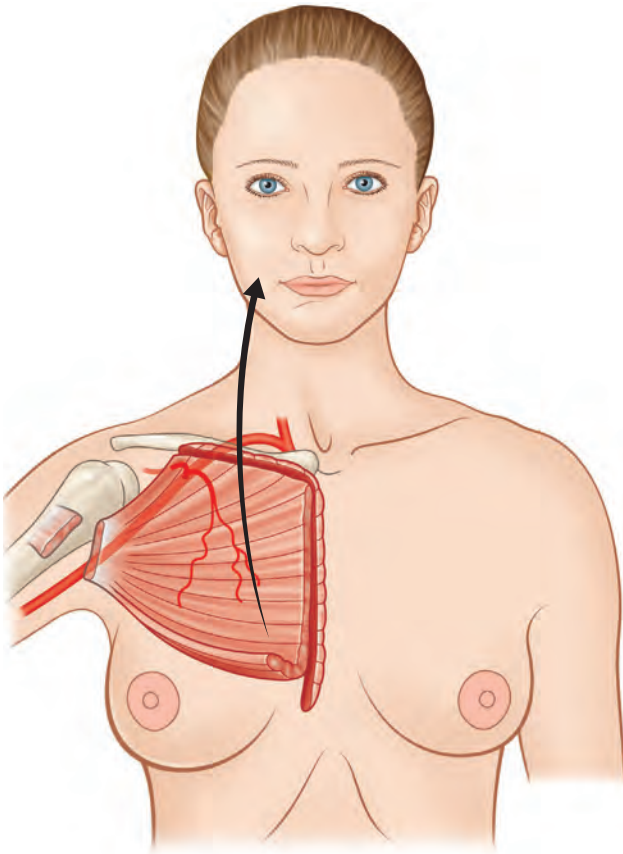


Fig. 22.49 Pectoralis major flap. Standard arc to middle third of face.

reconstruction. Historically, the trapezius has also been used as an osteomusculocutaneous flap, incorporating either the lateral aspect of the clavicle or the spine of the scapula (Figs. 22.51 & 22.52).²⁰⁶

The latissimus dorsi is a type V muscle originally described as a superiorly based flap by Tansini in 1896.²⁰⁷ Since the first

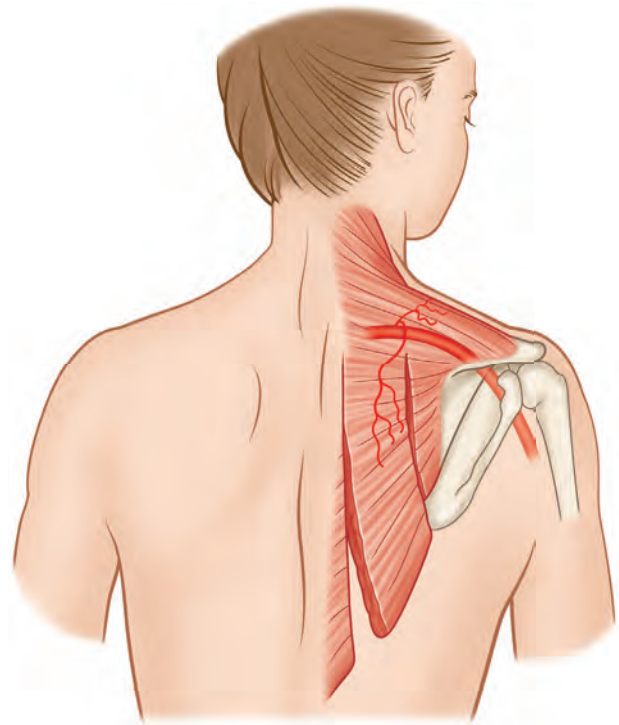


Fig. 22.51 Trapezius flap. Arc to face and anterior neck.

description, there have been numerous modifications and refinements of the flap. Historically, the latissimus dorsi musculocutaneous flap has been used in head and neck reconstruction for large defects or when previous irradiation or surgery precluded the use of other flaps. Since Quillen *et al.* reported the use of the latissimus dorsi as a transposition island flap in 1978 to cover the mandible and neck after resection of a tumor; various other clinical applications of the muscle have been described.²⁰⁸ In fact, the latissimus dorsi musculocutaneous flap was used frequently in intraoral and pharyngeal reconstruction.²⁰⁹ Other uses of the latissimus



Fig. 22.50 (A–C) Pectoralis major flap for head and neck reconstruction.



Fig. 22.52 (A–E) Vertical trapezius musculocutaneous flap for head and neck reconstruction.

dorsi muscle in head and neck reconstruction have included reconstruction of defects of the posterior neck, shoulder, anterior neck, lower face, occipital scalp, and intraoral-pharyngoesophageal regions.

The main impact of perforator flaps in the head and neck region is the increased capability of these flaps to accommodate complex reconstructions. The addition of perforator flaps with enhanced knowledge of vascular anatomy has allowed increased versatility in choosing an appropriate flap. The facial artery perforator flap is an example of increased choice for reconstruction of head and neck.²¹⁰ It is an evolved form of nasolabial flap and overcomes the limitations by providing a thinner flap, does not need a second procedure of dividing the flap, and provides a better rotation and mobility (Fig. 22.53). The second advantage of perforator flaps in the head and neck is the increased availability of donor site options. The submental perforator flap based on the perforator of the submental artery provides excellent texture, color match and hair-bearing properties ideal for head and neck reconstruction

(Fig. 22.54).^{211,212} The pedicle can be long as 8 cm, reaching temporal, midface, lower face as well as the oral cavity.²¹³ Depending on the laxity of the skin, it can be closed primarily and the scar well hidden in the cervicomental angle.

Breast reconstruction

Regional flaps:

1. Pectoralis major
2. Serratus anterior
3. Pectoralis minor.

Distant flaps:

1. Rectus abdominis
2. Latissimus dorsi.

Perforator flap:

1. Lateral intercostal artery perforator

Muscle and musculocutaneous flaps have had a tremendous impact on breast reconstruction and have provided women



Fig. 22.53 The facial artery perforator flap is an evolved form of nasolabial flap and overcomes the limit by providing a thinner flap, does not need a second procedure of dividing the flap and provides a better rotation and mobility of the flap.

with superior cosmetic results after mastectomy. Less aggressive surgical treatment of breast cancer such as the modified radical mastectomy, skin or nipple-sparing mastectomy, and lumpectomy have replaced the classic radical mastectomy as the treatment of choice for breast cancer. This change in

approach has resulted in smaller defects and more local tissue available for use in reconstruction. In addition, more women with pre-malignant disease or with a family history of breast cancer are undergoing prophylactic mastectomy and immediate reconstruction.

Local muscles available in breast reconstruction are the pectoralis major, pectoralis minor and serratus anterior. These muscles are especially important for patients who undergo prosthetic implant or expander insertion. For patients with an intact pectoralis major muscle and adequate overlying skin, the submuscular (subpectoral or subserratus-pectoral) placement of a prosthetic implant is a common reconstructive technique.²¹⁴ The pectoralis minor and serratus muscles can also assist in implant coverage and are generally used in addition to the pectoralis major muscle.²¹⁵⁻²¹⁷

The distant muscles available in breast reconstruction include the latissimus dorsi, rectus abdominis and a variety of other muscles transferred microsurgically including the gluteus, and fasciocutaneous perforator flaps (deep inferior epigastric perforator, superficial inferior epigastric artery and transverse upper gracilis). Distant musculocutaneous or fasciocutaneous flaps are usually indicated for patients with inadequate local tissue, unacceptable overlying skin, or radiation damage.



Fig. 22.54 The submental perforator flap based on the perforator of the submental artery provides excellent texture, color match and hair-bearing properties ideal for head and neck reconstruction.

Tansini described the earliest version of the latissimus flap.²⁰⁷ Since then, this muscle has become one of the most versatile flaps in plastic and reconstructive surgery. The advantages of the latissimus flap are that it has a reliable vascular supply and skin island and ultimately provides an acceptable cosmetic result.²¹⁸ The major drawback in using the latissimus dorsi muscle for breast reconstruction is that a prosthetic implant is usually required to provide adequate projection, as the musculocutaneous flap by itself is generally too thin.²¹⁹ Given this, the extended latissimus dorsi flap has been described; it provides additional soft tissue, thus obviating the need for implants.²²⁰ In addition, the latissimus dorsi donor scar is often unsightly and the seroma rates high.²²¹

The rectus abdominis is a type III muscle that commonly supplies a generous amount of abdominal fat and overlying skin. As a musculocutaneous flap, the rectus abdominis has proved to be one of the most valuable options for breast reconstruction. Variations in flap design have produced different types of rectus abdominis musculocutaneous flaps (e.g., vertical, transverse, bipedicle, superiorly based, and inferiorly based flaps). The flap was initially described based on its superior pedicle, the superior epigastric artery and venae comitantes, with a vertical skin island. Subsequently, its use based on the inferior pedicle, the deep inferior epigastric artery, was reported.²²² In 1982, Hartrampf *et al.* described a technique that changed the entire approach to breast reconstruction.²²³ By alignment of the skin island in a transverse direction, between the umbilicus and pelvis, the rectus abdominis musculocutaneous flap provided skin and soft tissue for breast reconstruction with improved abdominal contour. The transverse rectus abdominis musculocutaneous (TRAM) flap is now considered the musculocutaneous flap of choice for breast reconstruction (Fig. 22.55).

The indications for using the TRAM flap in breast reconstruction include a patient in need of additional soft tissue and overlying skin who has a moderate amount of lower abdominal tissue; a patient who prefers autologous tissue reconstruction without the use of a prosthetic implant; a patient who prefers a lower abdominal donor scar rather than a back scar; and a patient who has had an unacceptable result after undergoing other reconstructive methods (Fig. 22.56).²²⁴

The relative contraindications to using the TRAM flap include an extremely thin patient who has little lower abdominal tissue, a nulliparous patient in her child-bearing years, a patient with a history of abdominal wall hernia, an extremely obese patient, a heavy smoker, and a patient with lower abdominal scars. An absolute contraindication for a superiorly based transposition TRAM flap for breast reconstruction is prior division of its superior pedicle, usually related to a superior transverse laparotomy incision.

The advantages of the TRAM flap include the following:

1. It provides sufficient bulk so that a prosthetic implant usually is not required.
2. The suprapubic horizontal donor scar is aesthetically acceptable.
3. Transposition of the flap can be performed with the patient in a single operative position.
4. The skin dimensions are larger than those available with the latissimus dorsi flap.
5. A simultaneous abdominoplasty is accomplished with direct donor site closure.

The major disadvantage of the TRAM flap is that there is a potential risk of abdominal hernia or weakness after the use of the unilateral or bilateral rectus muscles for flap harvest.²²⁵

The long-term effect of the loss of one or both rectus abdominis muscles has been the subject of many investigations.²²⁶ Most studies report qualitative rather than quantitative data with regard to the postoperative strength of the abdominal wall. However, studies are beginning to show qualitative deficits of abdominal wall muscle loss.²²⁷ Overall, the majority of patients resume normal activities, without physical limitations, after breast reconstruction with the TRAM flap.

For breast reconstruction, TDAP (thoracodorsal artery perforator), AICAP (anterior intercostal artery perforator), LICAP (lateral intercostal artery perforator), and SEAP (superior epigastric artery perforator) flaps can be used as regional flaps. These regional flaps may serve to reconstruct the breast after partial mastectomy. The LICAP flap is frequently used for reconstruction for lower lateral quadrant partial mastectomy defects. They can be a simple alternative to pedicled latissimus dorsi flaps or TDAP flaps.²²⁸ The LICAP flap is supplied by the lateral branch of posterior intercostal artery found at the junction of the midaxillary line and the lower border of the corresponding rib. Perforators rising between the fourth and sixth intercostal are ideal options for partial breast reconstruction (Fig. 22.57).

Mediastinum

Regional flaps:

1. Pectoralis major.

Distant flaps:

1. Rectus abdominis
2. Latissimus dorsi
3. Omentum.

The most common reason for reconstructing the mediastinum is infection after median sternotomy. Although the incidence of infection following median sternotomy is low, reported from 0.4% to 6.9%, the morbidity and mortality are significant.²²⁹ The treatment of an infected median sternotomy wound depends on the extent of the infection and the amount of tissue necrosis. Historically, the standard therapy for an infected median sternotomy wound included debridement and closed tube irrigation. Muscle flap coverage was generally reserved for wounds recalcitrant to standard therapy. Now, it is generally accepted that early muscle flap transposition decreases morbidity, and therefore the use of a muscle flap should always be considered for the treatment of median sternotomy wounds.

The preferred local muscle for mediastinal coverage is the pectoralis major. In 1980 Jurkiewicz *et al.* described the use of the pectoralis major muscle flap to obliterate the sternal-mediastinal dead space.²³⁰ The pectoralis major can be mobilized in several ways. The muscle can be transposed either on the dominant thoracoacromial pedicle or as a turnover flap on the segmental secondary vascular pedicles (perforating vessels from the internal mammary artery and vein). Nahai *et al.* described a modified technique of the turnover flap that preserves the lateral one-third of the muscle based on the dominant vascular pedicle and its motor nerves.²³¹ The advantage of this technique is the preservation of the anterior

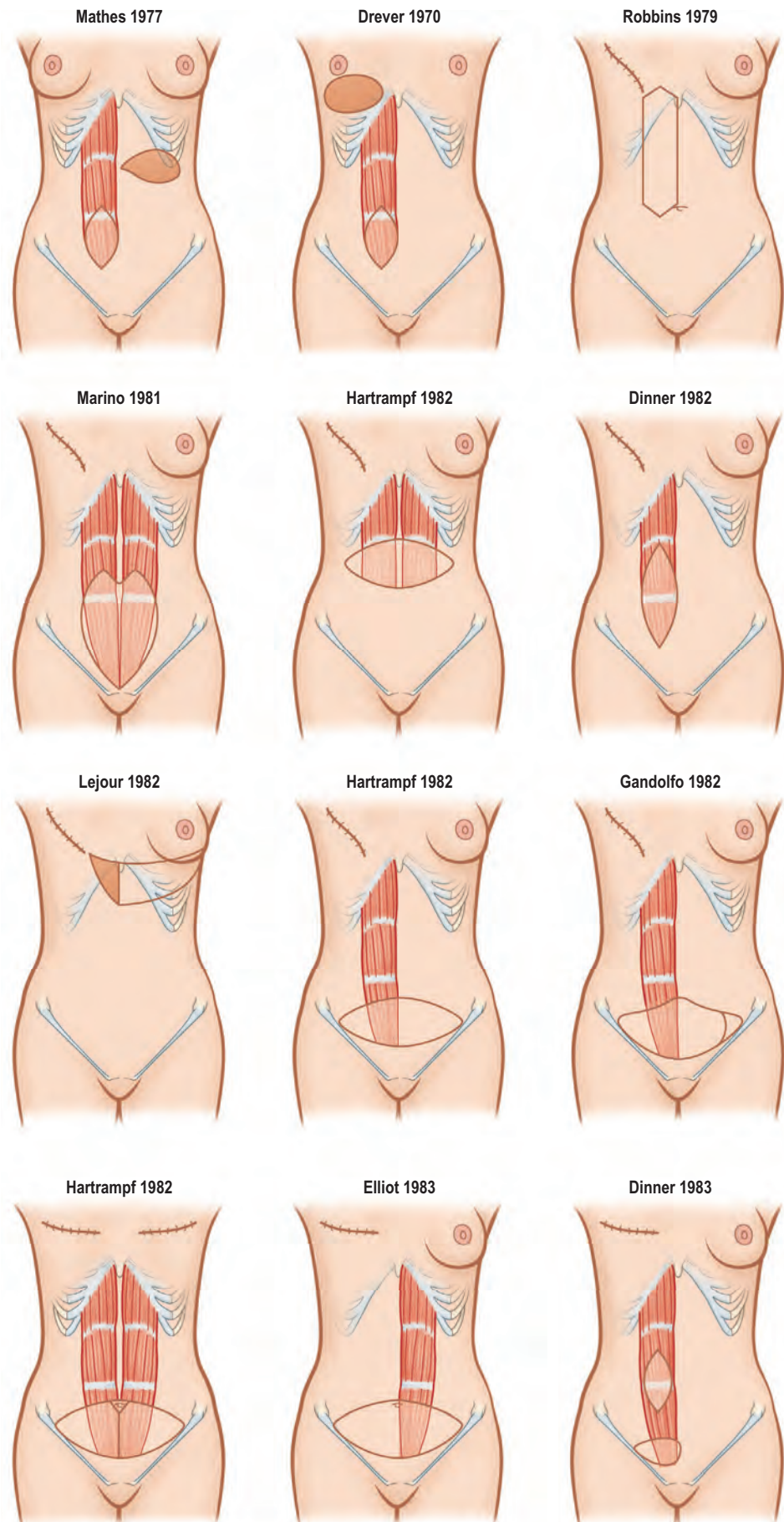


Fig. 22.55 Various designs of superiorly pedicled TRAM flaps.



Fig. 22.56 (A–C) TRAM flap breast reconstruction.

axillary fold. The pectoralis muscle flap remains the mainstay of treatment in both adults and children with sternal wound infections.^{232–234}

Depending on the size of the defect, the surgeon can use one or both pectoralis major muscles for coverage.²³⁵ If additional coverage is needed, the rectus abdominis can be used

along with the pectoralis major muscles to cover the inferior aspect of the wound.²³⁶ Used as either a muscle or musculocutaneous flap, the rectus abdominis muscle is a reliable source for inferior mediastinal coverage; in addition, it provides the ability to fill a large dead space.^{237,238} In considering the use of the rectus abdominis muscle, it must be noted that the superior epigastric artery is the continuation of the internal mammary artery inferior to the sternum that should be avoided during debridement of the sternal wound. Furthermore, the use of the internal mammary artery as a coronary artery bypass graft may adversely affect perfusion of the superiorly based rectus abdominis flap, which precludes the use of the rectus flap on that side. Collateral circulation to the internal mammary vessels distal to the site of ligation during coronary bypass will generally allow adequate perfusion through the superior epigastric artery and vein for superior transposition to the mediastinum (Figs. 22.58 & 22.59).

The omentum is an alternative source of tissue available to be transferred for mediastinal reconstruction; it may be used solely or in combination with another flap.²³⁹ The omentum can be based on the right or left gastroepiploic vessels. In view of the risk of exposing the peritoneum to a contaminated field, however, the omentum is generally reserved for patients in whom the pectoralis major and rectus abdominis muscles are unavailable.²⁴⁰ The harvest of the omentum has been achieved laparoscopically to lower the potential abdominal wall morbidity.²⁴¹

The latissimus dorsi provides another alternative muscle or musculocutaneous flap for coverage of the upper mediastinum.²⁴² Its use is usually indicated when the pectoralis major is absent or damaged by previous incisions or radiation therapy.²⁴³ The advantage of using the latissimus dorsi muscle or musculocutaneous flap is that the vascular pedicle and the donor site are distant to the infected area.²⁴⁴ The disadvantages include the inconvenience of obtaining a muscle flap from the back and that the latissimus dorsi muscle may be too thin for the deeper, more extensive mediastinal defects. The latissimus dorsi can also be transferred microscurgically to sternal wound defects.²⁴⁵

Chest wall and pulmonary cavity

Regional flaps:

1. Pectoralis major
2. Latissimus dorsi
3. Serratus anterior.

Distant flaps:

1. Rectus abdominis
2. Omentum.

Perforator flaps

1. TDAP (thoracodorsal artery perforator)
2. Keystone flaps.

Reconstruction of the chest wall is challenging. Ablative surgery for neoplasm, infection, radiation, and trauma can produce extensive full-thickness chest wall defects. Furthermore, many of the patients in need of reconstruction have previously undergone some form of chemotherapy or high-dose irradiation for their primary disease. Wound healing can therefore be severely compromised at the time of reconstruction.

Historically, methods of chest wall reconstruction consisted of various random and tube flaps that often required several stages before completion. Currently, the reconstruction of the chest wall is successfully accomplished without the need for delay or staged procedures. Partial thickness defects with

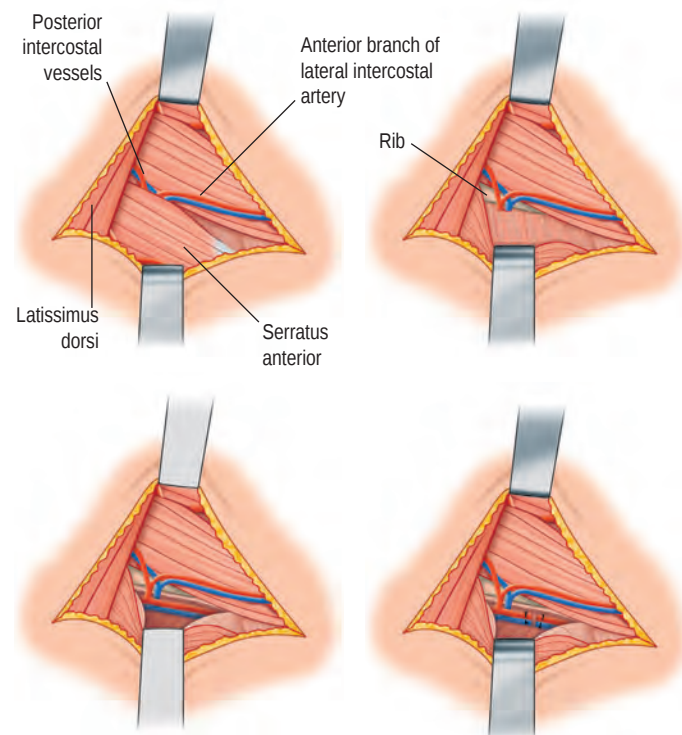
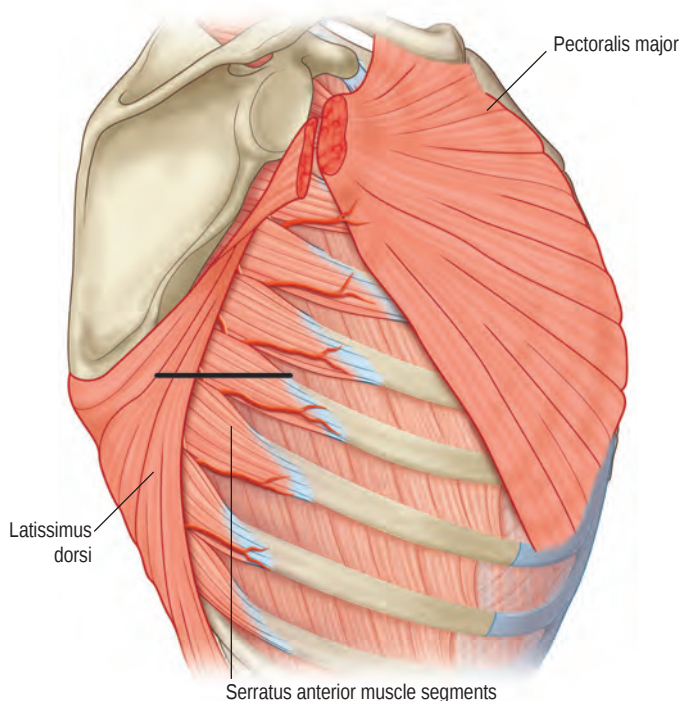


Fig. 22.57 The LICAP flap is supplied by the lateral branch of the posterior intercostal artery found at the junction of the midaxillary line and the lower border of the corresponding rib. Perforators rising between the fourth and sixth intercostal are ideal options for partial breast reconstruction.

viable muscle at the wound bed can be managed with skin grafting; larger full-thickness defects require flap reconstruction. In addition to flap reconstruction, Prolene® mesh is indicated for chest wall reconstruction to provide stability and support for the overlying flap when there is significant loss of chest wall continuity.^{246,247}

The pectoralis major and latissimus dorsi muscle and musculocutaneous flaps are the most commonly used in chest wall reconstruction. Larson and McMurtrey stated that the pectoralis major musculocutaneous flap is the flap of choice for defects of the lower neck and upper third of the sternum, whereas the latissimus dorsi musculocutaneous flap is preferred for wounds of the anterior chest wall that will require removal of two or three ribs and resection of <8 cm of skin. In these authors' series of 53 flaps in 50 patients, the musculocutaneous flap alone provided adequate support and stability. Fascia, ribs, and prosthetic mesh were not needed for support.²⁴⁸

The use of the latissimus dorsi flap in a patient who has previously undergone a thoracotomy decreases the reliability of the pedicle and safety of subsequent ipsilateral flap transposition although previous thoracotomy is not an absolute contraindication. In fact, Scheffan *et al.* reported that a standard anterolateral thoracotomy, which separates the latissimus

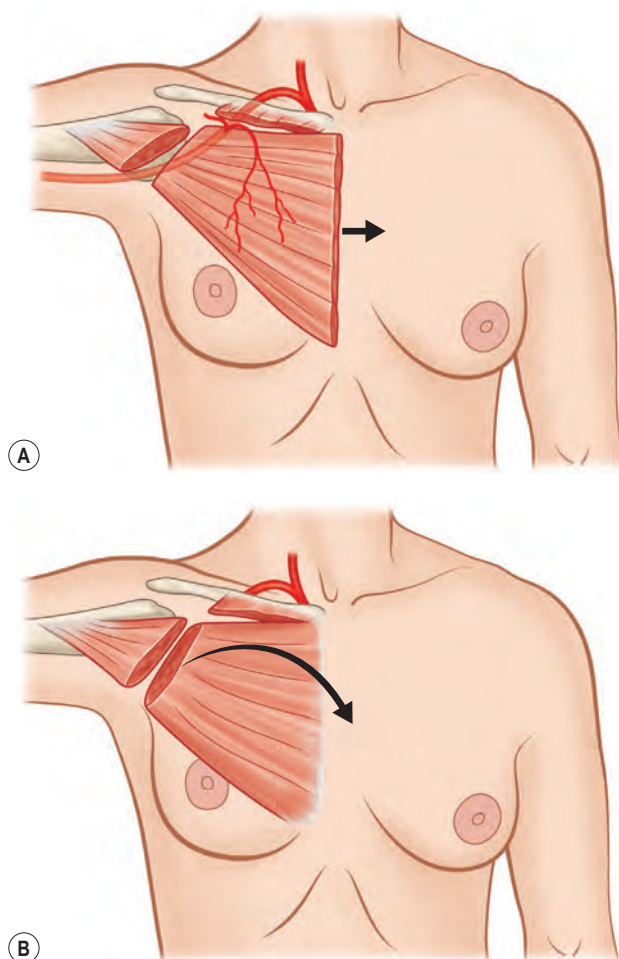


Fig. 22.58 Pectoralis major flap. (A) Standard flap to anterior mediastinum based on thoracoacromial pedicle. (B) Turnover arc to anterior mediastinum based on perforator vessels from internal mammary artery and associated veins.

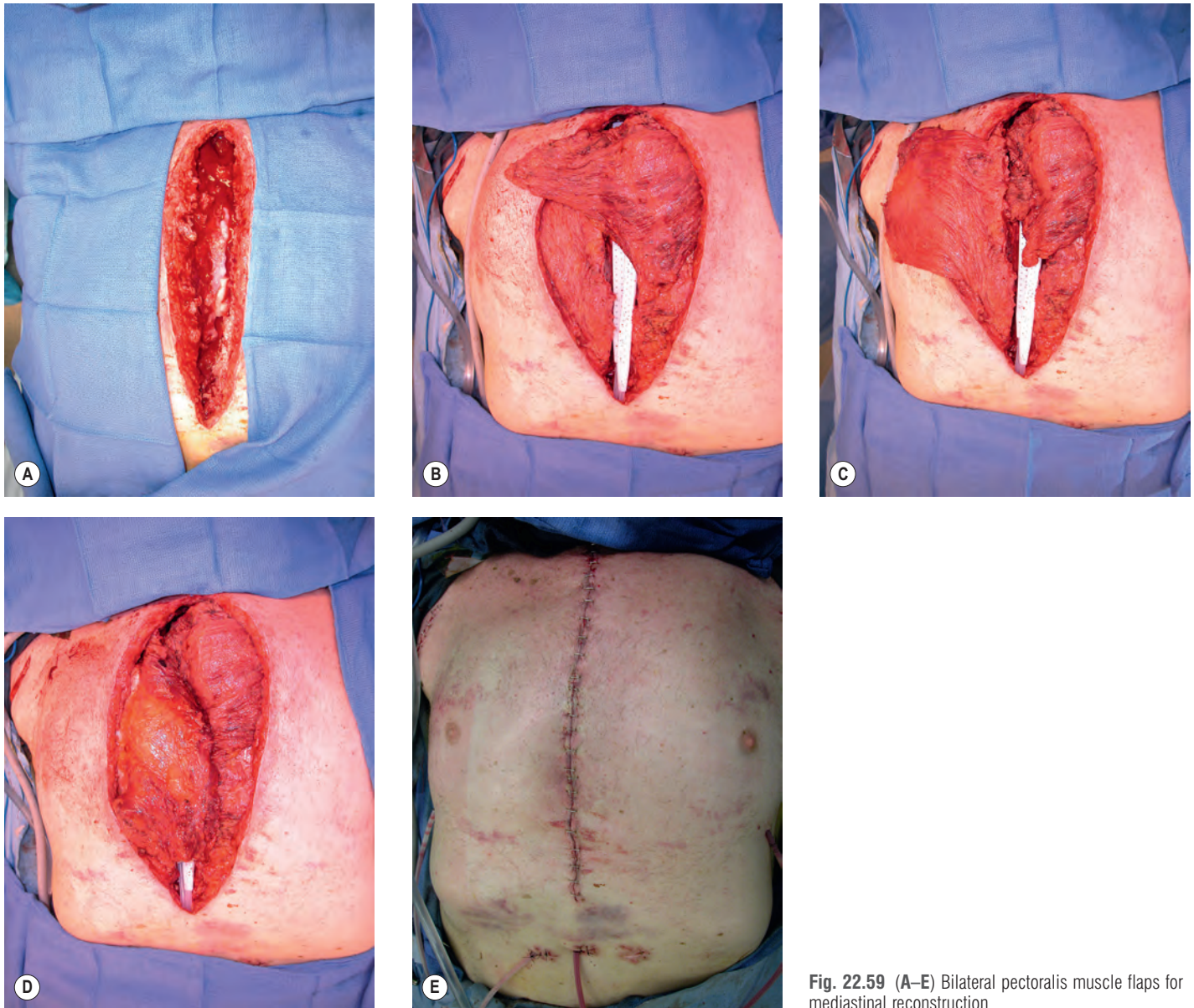


Fig. 22.59 (A–E) Bilateral pectoralis muscle flaps for mediastinal reconstruction.

dorsi into an upper third and lower two-thirds, does not preclude the subsequent use of the muscle as a flap.²⁴⁹ More recently, the latissimus dorsi muscle has been used successfully in patients who had undergone previous posterolateral thoracotomy.²⁵⁰ The upper third of the latissimus dorsi muscle, based on the thoracodorsal pedicle, may be used to cover superior anterolateral chest wall defects. The lower two-thirds of the muscle, based on its secondary pedicles from the paraspinal perforators, can be used as a reverse latissimus dorsi flap with or without the overlying skin to cover inferolateral and posterior chest wall defects. Early work by McCraw *et al.* and Bostwick *et al.* was instrumental in the development of the reverse latissimus dorsi flap.^{251,252} Latissimus dorsi muscle and musculocutaneous flaps have proved invaluable in the treatment of numerous chest wall and pulmonary cavity disorders including Poland syndrome,^{253,254} spina bifida defects,^{255,256} and diaphragmatic hernias.^{257,258}

The serratus anterior muscle can also be useful as a local muscle flap for chest wall and pulmonary cavity

reconstruction. The serratus muscle has a constant and reliable vascular pedicle and a long arc of rotation.²⁵⁹ Arnold *et al.* described its use in reconstructing the chest wall, closing bronchopleural fistulas, and reinforcing tracheal reconstructions.²⁶⁰ The serratus may be surgically split thereby utilizing only a portion for reconstruction.⁴⁴

The rectus abdominis muscle is a distant muscle or musculocutaneous flap for chest wall reconstruction. Larson *et al.* showed that the rectus abdominis musculocutaneous flap is particularly useful for large chest wall defects.²⁴⁸ The availability of the flap is dependent on the status of the internal mammary arteries. Miyamoto *et al.* favored the rectus abdominis musculocutaneous flap over the latissimus dorsi in chest wall reconstruction because of its convenience (the patient can remain in one position intraoperatively), ease of elevation and subsequent closure of the donor site.²⁶¹ In addition, it is thought that in situations when up to three ribs are removed and reconstructed with mesh, the rectus shows a distinct advantage given its thickness which

minimizes the risk of creating a flail chest wall.²⁶² Large defects of the chest wall within the arc of rotation of the rectus can be reconstructed. The rectus abdominis muscle may be used as a transverse or vertically oriented musculocutaneous flap.²⁶³

If the internal mammary vessels have been manipulated the rectus flap is often transferred microsurgically.²⁶⁴

The omentum is also utilized for chest wall reconstruction. The omentum can be harvested laparoscopically, obviating the need for a large abdominal incision. When used as a transpositional flap, the omentum can be based on either the right or left gastroepiploic vessels. The omentum has a large surface area, obliterates dead space, is pliable, and contains angiogenic and immunogenic properties. The use of the omentum in chest wall reconstruction secondary to osteo-radionecrosis, cancer ablation, and chronic wounds is well established.⁷⁹

The regional perforator flaps are often with short pedicle around the chest. The TDAP flap does have a long pedicle making reconstruction possible in the upper two thirds of the chest wall. However, the frequent presence of dead space may require additional muscle mass favoring the latissimus musculocutaneous flap. The keystone island flap based on fasciocutaneous and musculocutaneous perforators offers robust vascularity of perforator flaps and the ease and speed of simple local flap advancement.³²

Abdominal wall

Regional flaps:

1. Rectus abdominis
2. External oblique.

Distant flaps:

1. Tensor fascia lata
2. Latissimus dorsi
3. Rectus femoris.

Perforator flaps:

1. Anterolateral thigh (ALT)
2. Deep inferior epigastric artery perforator (DIEAP)
3. Deep superior epigastric artery perforator (DSEAP)
4. Propeller.

In reconstructing abdominal wall defects, the surgical objective is to provide soft tissue coverage in addition to re-establishing the abdominal wall integrity. To plan safe and reliable techniques for wound closure, it is helpful to classify complex wounds by location and the status of the overlying skin and soft tissue coverage. In regard to location, the abdominal wall is divided into four zones: zone 1A, upper midline defects with extension across the midline; zone 1B, lower midline defects with extension across the midline; zone 2, upper quadrant defects; and zone 3, lower quadrant defects (Fig. 22.60, Table 22.14).

The two muscles available for local flaps are the rectus abdominis and the external oblique. The rectus abdominis muscle or musculocutaneous flap is the flap of choice for unilateral abdominal wall defects. In 1977 Mathes and Bostwick described the use of the rectus abdominis musculocutaneous flap for reconstruction of an abdominal wall defect.²²² Parkash and Ramakrishnan reported the use of a rectus abdominis musculocutaneous island flap for coverage of an extensive radionecrotic abdominal wall ulcer that had been

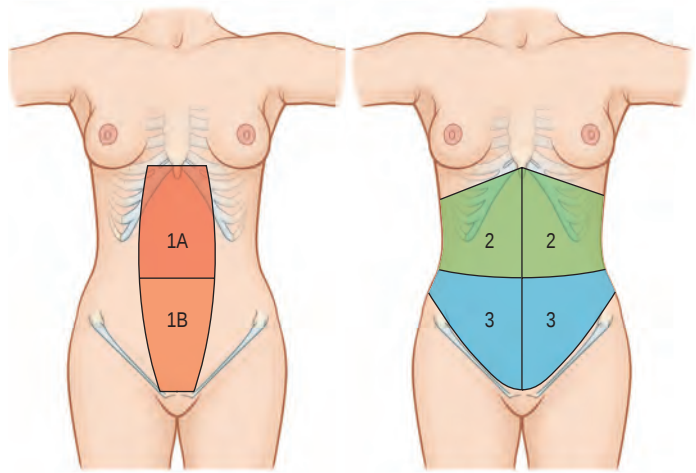


Fig. 22.60 Reconstructive zones of the abdomen.

resistant to conservative therapy.²⁶⁵ In 1983, Taylor *et al.* described the extended deep inferior epigastric flap, which consists of an inferiorly based rectus abdominis musculocutaneous flap with a superolateral fasciocutaneous extension. With this larger skin territory, extensive defects of the abdomen, as well as those of the groin and thigh, have been successfully treated.²⁶⁶

The rectus may be released from its lateral attachments to achieve midline abdominal wall closure. Several variations have been described. One variety, termed separation of components, involves separation of the external oblique fascia with an incision just lateral to the linea semilunaris allowing a plane to develop between the external and internal oblique muscles.²⁶⁷ This permits medial mobility of the rectus abdominis muscle. Other variants of sliding myofascial partitions or releases have been used successfully to reconstruct the abdominal wall.^{222,268} Alternatively, the rectus may be used as a turnover flap to achieve closure.²⁶⁹

The external oblique muscle may be used to reconstruct absent or deficient rectus fascia.²⁷⁰ The external oblique musculocutaneous flap is an alternative local flap, useful for

Table 22.14 Flaps for abdominal reconstruction by location (zone)

Flaps	Zones			
	1A	1B	2	3
Latissimus dorsi			X	
Rectus abdominis				
Superiorly based	X		X	
Inferiorly based		X		X
Advancement	X	X		
External oblique advancement				X
Tensor fascia lata				
Transposition		X		X
Expansion	X	X	X	X
Rectus femoris		X		X

(Modified from Mathes SJ, Steinwald PM, Foster RD, et al. Complex abdominal wall reconstruction: a comparison of flap and mesh closure. *Ann Surg.* 2000;232:586–596.)

reconstructing small, full-thickness upper abdominal wall defects.^{271–273} The external oblique musculofascia may also be expanded and advanced centrally to repair abdominal wall defects.^{274,275}

The distant muscle and musculocutaneous flaps used in abdominal wall reconstruction include the latissimus dorsi, tensor fascia lata, and rectus femoris flaps. Transposition of the latissimus dorsi musculocutaneous flap is a reliable technique that is particularly useful for superolateral abdominal wall defects.^{276,277} This flap is particularly useful in traumatic defects, burn injuries and post-extirpative defects.^{278–280} The latissimus dorsi can also be transferred microsurgically to cover central abdominal defects.²⁸¹ This flap may also be reinnervated and has shown enough contractile capacity and strength to adequately replace the function of the missing abdominal wall muscles.²⁸²

The use of the tensor fascia lata (TFL) as a musculocutaneous and musculofascial flap is indicated for lower abdominal wall reconstruction. Wangenstein initially described use of this flap for lower abdominal wall closure.²⁸³ The unique qualities of the tensor fascia lata flap include the large amount of vascularized fascia and skin and the low donor site morbidity.^{284–286} The TFL is most commonly used as a rotational flap, although success as a free flap has been demonstrated.²⁸⁷ As a rotational flap, the arc of rotation is limited to the lower abdominal wall, whereas when used as a free flap, any region of the abdominal wall may be reconstructed.²⁸⁸

The rectus femoris musculocutaneous flap is a dependable alternative flap for abdominal wall reconstruction.^{289,290} Variations of the rectus femoris flap, including the use of fascial extensions and tissue expansion, have been described to extend its arc of rotation.^{291,292} However, it tends to be bulkier than the TFL and has greater donor site morbidity. Leg extension may be adversely affected with the use of this flap although subsequent studies show no appreciable effect.^{291,293} In certain instances the rectus femoris is preferred to the TFL flap. An example would be the use of the rectus femoris to treat a radionecrotic ulcer involving the lower abdominal wall, given the need for muscle bulk to fill the defect (Fig. 22.61).²⁹⁴

There can be many options for perforator flaps to cover the abdomen. For moderate or small-sized wounds, a perforator can be found near the defect and the flap can be rotated as a propeller flap to cover the skin defect of the abdomen. This rotation based on the perforator allows rotation of the flap without violating the structures beneath the deep fascia.⁵⁸ For larger and complex wounds, a larger perforator flap or a flap with composite tissue can be used. Fig. 22.62 divides the abdomen into five zones showing the preferred perforator flap for reconstruction.⁵⁸ The DIEP flap can be rotated as a propeller to cover the lower abdomen as well as the mid abdomen. If there is a scar within the flap territory, it may jeopardize the flap circulation after elevation. A pedicled ALT flap can be harvested with large dimensions able to reach the low and lateral abdomen. The ALT can be elevated with a deep fascia as a composite flap to restore the integrity of the abdominal wall.²⁹⁵ The DSEAP flap can be designed horizontal and slightly obliquely parallel to the costal margin. A propeller-style harvest and rotation can be done to reconstruct the upper abdominal region.⁵⁸ When elevating this flap, one should always confirm the presence of the internal mammary artery as this is the main source vessel of the perforator.

Groin and perineum

Regional flaps:

1. Sartorius
2. Pudendal thigh flap.

Distant flaps:

1. Gracilis
2. Tensor fascia lata
3. Rectus femoris
4. Rectus abdominis
5. Gluteus maximus.

Perforator flaps

1. Free-style perforator.

Reconstruction of the groin and perineum is often indicated for defects due to trauma, tumor resection and infection. The wounds can be extensive and, because of their proximity to the anus and urethra, are susceptible to fecal and urinary contamination. In addition, wounds involving the groin may expose the femoral vessels. Vascular prosthetic grafts and adjunctive radiation therapy in the cancer patient can further compound the problem.

The sartorius is a type IV muscle with multiple segmental vascular pedicles that limit its arc of rotation. The division of one or two of the most proximal pedicles, however, enables the superior aspect of the sartorius muscle to be transposed medially into the groin. This technique is used for coverage of exposed femoral vessels and prosthetic vascular grafts.²⁹⁶

The pudendal thigh flap is an axial pattern, sensate fasciocutaneous flap based on the terminal branches of the internal pudendal artery.^{297,298} Variants of this flap are gluteal fold flaps, lotus flaps, and Singapore flaps.^{297,299,300} Various designs can be used: along the longitudinal axis in the line of the internal pudendal artery in the gluteal fold, a V-Y advancement, and a rhomboid-style flap.

The gracilis is a type II muscle that has both an anterior and posterior arc of rotation. Anteriorly, the muscle can be used for groin and perineal reconstruction; posteriorly, ischial and perirectal defects can be reconstructed.^{301–303} Other common uses of the gracilis muscle and musculocutaneous flap include reconstruction of the vagina, penis, scrotum, and anal sphincter (Fig. 22.63).^{294,304–306}

The tensor fascia lata (TFL) is particularly useful for groin and perineal reconstruction.^{307,308} It can be used as either a musculocutaneous flap or a musculofascial flap. The TFL is also used in vulvar reconstruction and recurrent inguinal hernia reconstruction.²⁸⁴

The rectus femoris is useful for coverage of the groin and perineum.^{309,310} It is a large, bulky muscle that has an arc of rotation similar to that of the tensor fascia lata. Despite its reliability and desirable muscle bulk, this muscle is generally used as an alternate flap in the ambulatory patient, given the potential functional deficit associated with its harvest, although more recent evidence suggests that the results of the reconstruction appear to outweigh the loss of strength.^{284,311}

The rectus abdominis muscle or musculocutaneous flap based on its inferior pedicle provides a reliable flap for defects of the anterior pelvis and groin.^{222,294,312} Its wide arc of rotation and abundant blood supply through the inferior epigastric vessels make it an excellent reconstructive flap for this region. The vertical rectus abdominis musculocutaneous

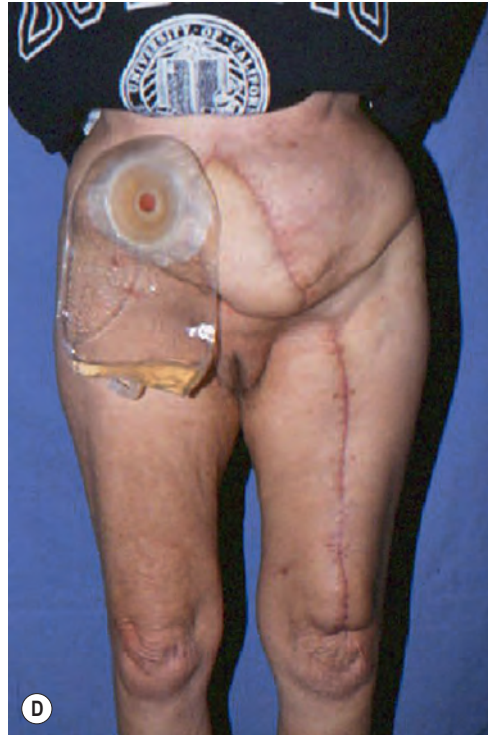
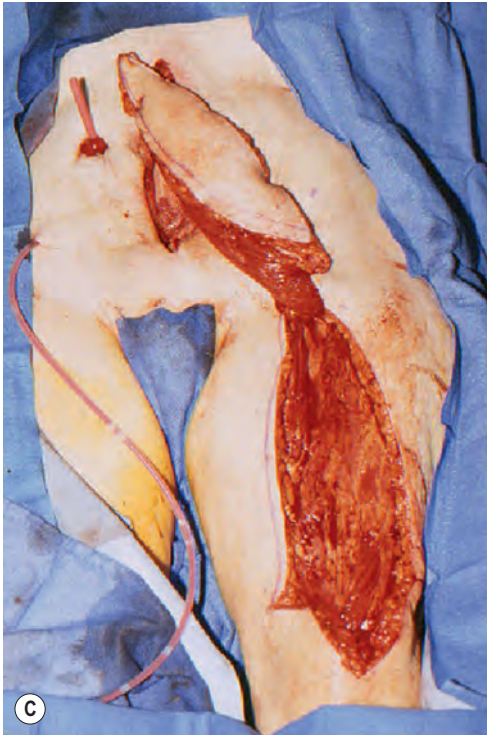
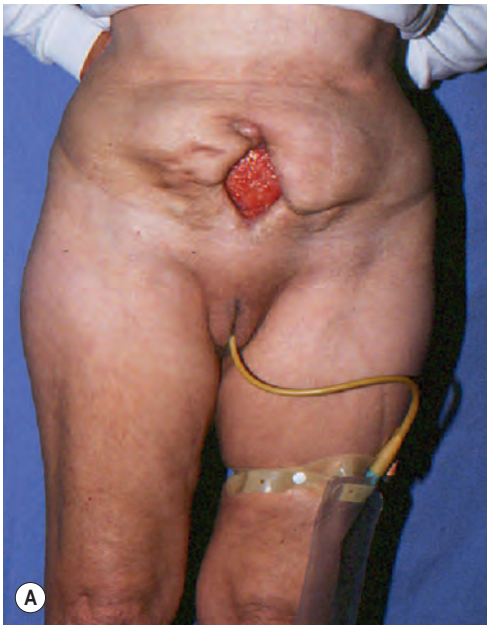


Fig. 22.61 (A–D) Rectus femoris musculocutaneous flap with intraperitoneal mesh for management of a chronic type II, zone 1B defect.

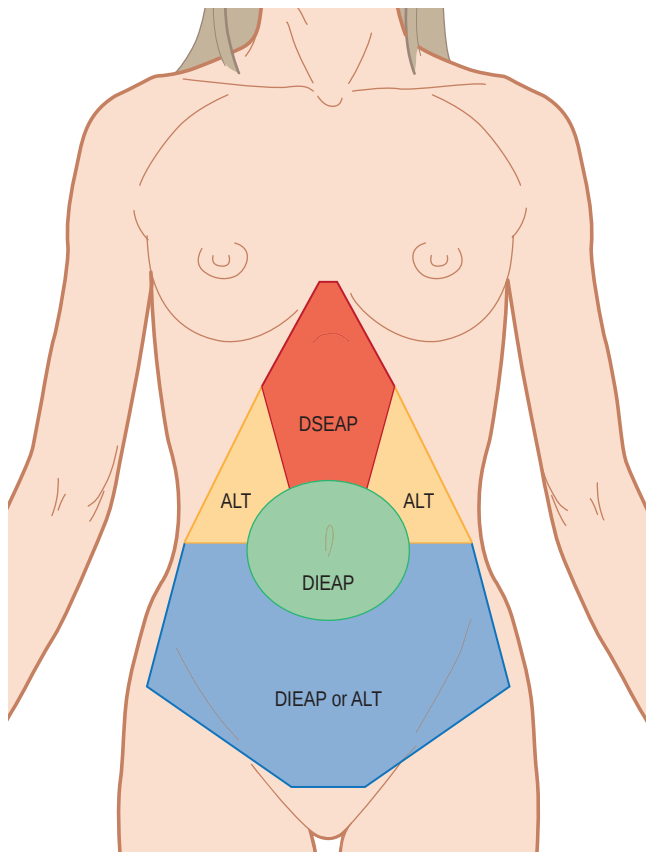


Fig. 22.62 The five zones of the abdomen are the periumbilical hub (green), the epigastric (red), left and right lateral (yellow), and infraumbilical (blue). They are shown with the preferred perforator flap for cutaneous coverage inscribed. ALT, anterolateral thigh; DIEAP, deep inferior epigastric artery perforator; DSEAP, deep superior epigastric artery perforator. (From Blondeel PN, Morris SF, Hallock GG, Neligan PC. *Perforator Flaps*, 2nd edn. St. Louis: QMP; 2013.)

flap is useful for large, irradiated defects in the perineum (Figs. 22.64 & 22.65).^{178,313,314}

The gluteus maximus muscle provides stable coverage for pelvic and perineal defects. Its large mass is particularly useful for obliterating pelvic dead space and covering perineal wounds; it is also useful for rectal sphincter reconstruction.^{315,316} The gluteus maximus fasciocutaneous V-Y advancement flap is reliable for extensive vulvectomy and recurrent rectal cancer defects (see Fig. 22.63).^{317,318} The gluteal thigh flap, described by Hurwitz, includes the inferior part of the gluteus maximus muscle and a large cutaneous territory of the posterior thigh that is supplied by the descending branch of the inferior gluteal artery.³¹⁹ The gluteus maximus musculocutaneous and gluteal fasciocutaneous flap is particularly useful for reconstructing deep perineal and pelvic defects.^{320,321}

Often perineal reconstruction can be complex, requiring multiple flaps. One must decide the best choice of reconstruction as well as considering ideal donor sites. Due to the rich available perforators of this region, many new flaps and approaches have been introduced.^{322,323} These perforator flaps can originate from the external and internal pudendal artery, obturator artery, deep inferior epigastric artery, inferior gluteal artery, descending branch of medial circumflex femoral artery, and more. One can design a single or a multiple perforator flap based on these perforators and tailor the reconstruction according to the needs of the defect. This free-style approach

allows choosing a well-vascularized skin flap, thin flap, provides a variety of flap design, and minimizes donor site morbidity.

Lower extremity

Regional flaps:

1. Gastrocnemius
2. Soleus.

Distant flaps:

1. Cross-leg.

Perforator flaps:

1. Propeller flap
2. Distally based perforator flaps
3. Medial sural artery perforator (MSAP).

Reconstruction of the lower extremity remains particularly challenging. Defects including exposed joints and prostheses, infected bone, and fractures are common. Furthermore, the availability of adequate soft tissue for coverage is limited, particularly in the lower third of the leg.

There are two local sources of muscle or musculocutaneous flaps available for reconstruction of the leg, the gastrocnemius and the soleus muscles. The use of distant flaps involves microvascular transplantation of various muscles or perforator flaps depending on the size of the wound and surgeon's preference. Many muscles have been described, including the gracilis, latissimus dorsi, and rectus abdominis. In an effort to minimize donor site, the anterolateral thigh flap, deep inferior epigastric perforator flap and the superficial inferior epigastric artery perforator flaps may be used as well. Cross-leg flaps are also available but have largely been supplanted by either local muscle flaps or microvascular composite tissue transplantation.

The gastrocnemius is a type I muscle, consisting of a medial and a lateral head. Each head has a wide arc of rotation based on its single vascular pedicle (medial or lateral sural vessels). The gastrocnemius muscle or musculocutaneous flap is the flap of choice for coverage of the knee and for coverage of exposed bone or orthopedic hardware involving the upper two-thirds of the leg.^{324,325} Defects of the middle third of the leg can also be reconstructed with the gastrocnemius muscle.^{326–328} In patients with radical knee debridement and loss or disruption of the extensor mechanism, the gastrocnemius can be used to restore knee function (Figs. 22.66–22.67).³²⁹

The soleus muscle flap is utilized for reconstructing defects involving the middle third of the leg. The soleus muscle is the prime ankle plantar flexor and it serves to stabilize the ankle in ambulation by opposing dorsiflexion.³³⁰ Because of compensatory mechanisms, the use of the soleus muscle as a flap does not impair function. Function-preserving techniques such as muscle splitting is recommended if the soleus is used in a patient who does not have a functional medial and lateral gastrocnemius muscle.^{331,332} Defects of the proximal third can be reached by the soleus, but require extensive mobilization of the muscle.³³³ In the lower third of the leg, the soleus muscle can be used as a proximally or distally based flap. In this region, however, the soleus muscle flap is generally used for smaller defects (Fig. 22.68). Larger defects require microvascular tissue transplantation.

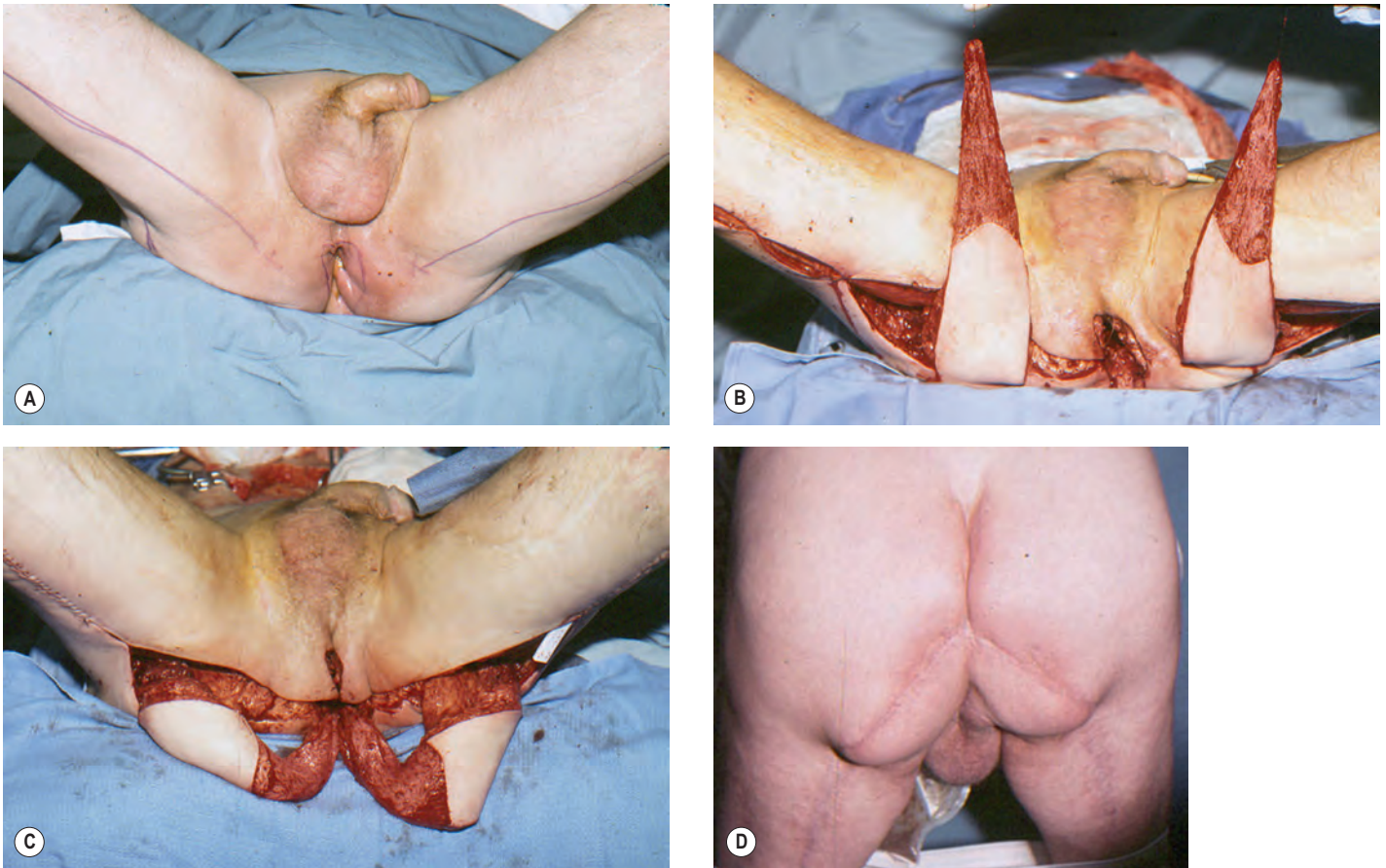


Fig. 22.63 (A–D) Bilateral gracilis and gluteal thigh flaps for reconstruction of a radiation defect of the perineum.

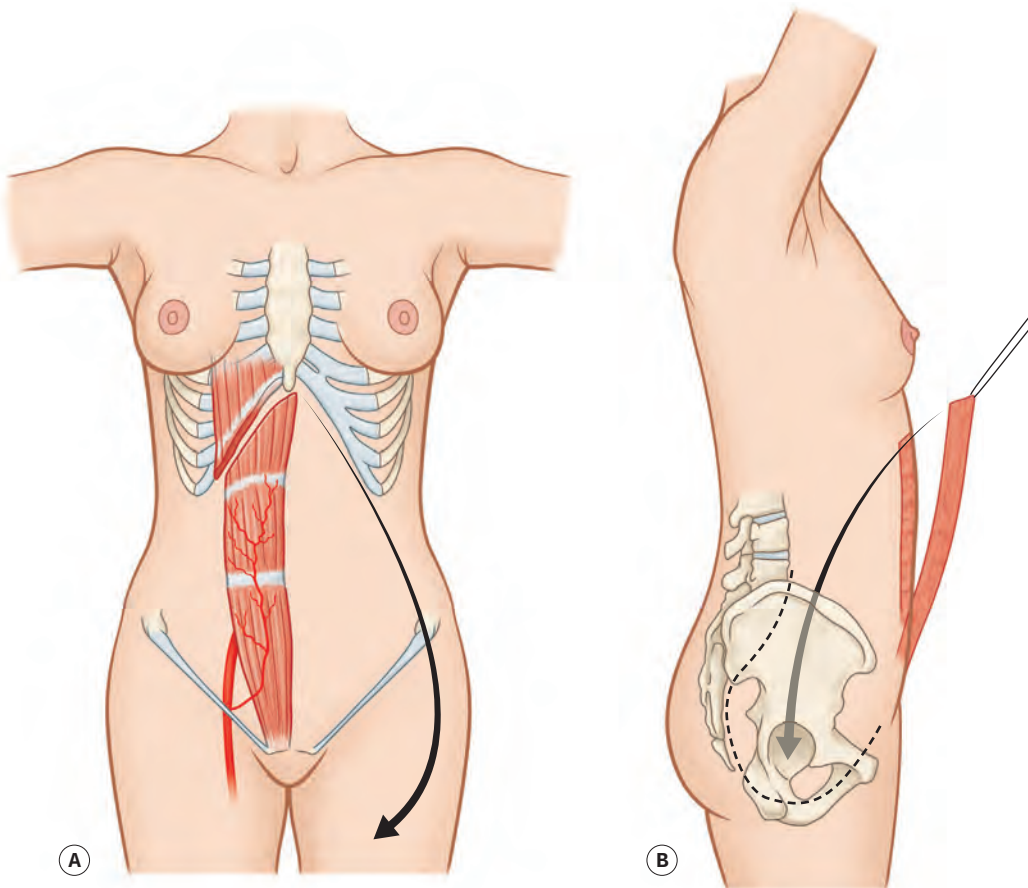


Fig. 22.64 Rectus abdominis flap. (A) Arc to perineum. (B) Arc to internal pelvis.

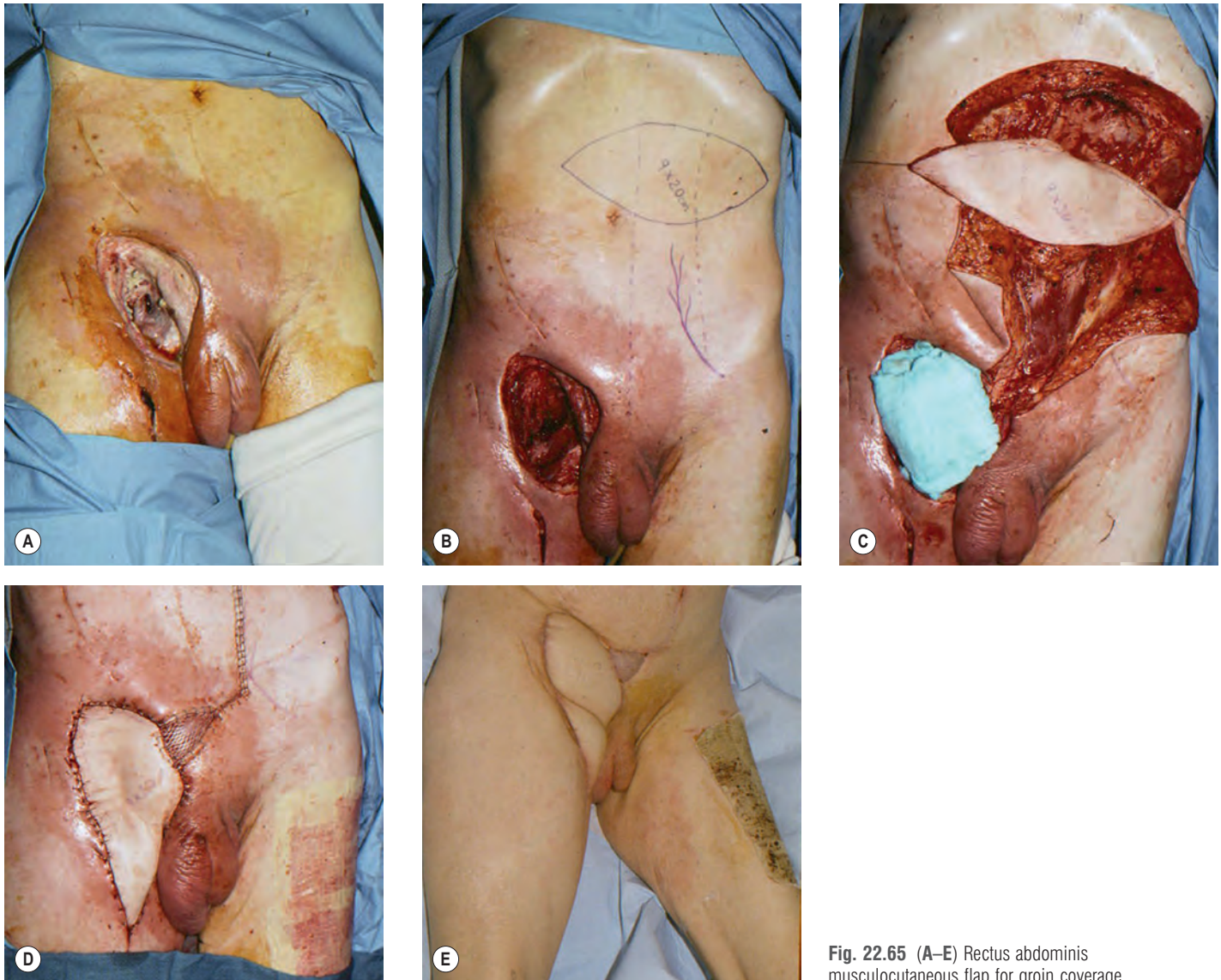


Fig. 22.65 (A–E) Rectus abdominis musculocutaneous flap for groin coverage.

For small and moderate-sized defects with less extensive dead space, a skin flap can be considered to restore function and form. The donor site is usually limited to the same extremity and the abundant perforators allow tailored reconstruction. The propeller flap based on a single perforator can be elevated as a fasciocutaneous or a skin flap harvested above the fascia. The flap is designed around a perforator as a pivot point and forming two blades with an unequal length that can be rotated to fill the defect (Fig. 22.69). The ability to rotate up to 180° makes it versatile for thigh and lower leg defects. Fig. 22.70 shows a free-style perforator-based propeller flap on the upper thigh rotated to reconstruct the mid posterior thigh defect after cancer resection. An adequate flap length can be secured by dissecting further into the source vessel when needed, injury to the perforator avoided with meticulous dissection, identification of a perforator with a good pulse, surrounding tissues around the perforators sufficiently released to minimize kinking, and supercharge or turbocharge veins located distally in the flap to reduce venous congestion. Although not ideal, skin graft on the donor site

may be needed when used in the lower leg. Nevertheless, the simplicity and versatility of this approach may justify the additional donor site morbidity. Some perforator flaps can be extended by making them reverse pattern/distally based flaps. When an ALT is elevated on a proximally located perforator and raised as a reverse pattern, the flap can easily reach the distal part of the knee.^{334,335} The MSAP flap is another flap that can reach the knee as a regional perforator flap. When a line is drawn from the midpoint of the popliteal crease to the apex of the medial malleolus, the first perforator from the medial sural artery usually rises from a semicircle with a 2 cm radius centered 8 cm distal to the popliteal crease (Fig. 22.71).³³⁶ With an average length of 8 cm, the flap can easily reach the knee.

Foot

Regional flaps:

1. Flexor digitorum brevis
2. Abductor hallucis

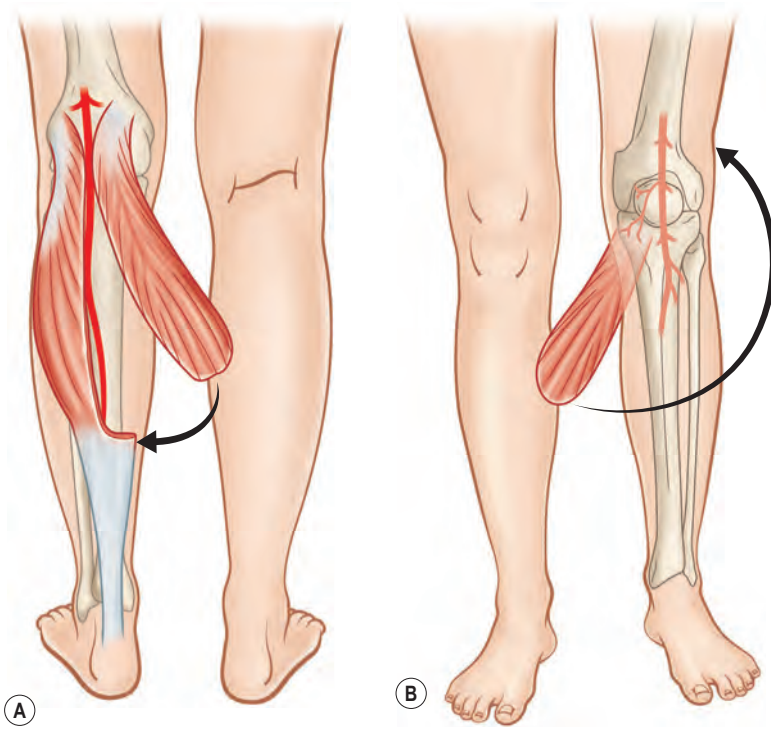


Fig. 22.66 Gastrocnemius flap. Arc to knee and upper third of leg.



Fig. 22.67 (A–D) Gastrocnemius musculocutaneous flap for knee and proximal third of tibia defect.

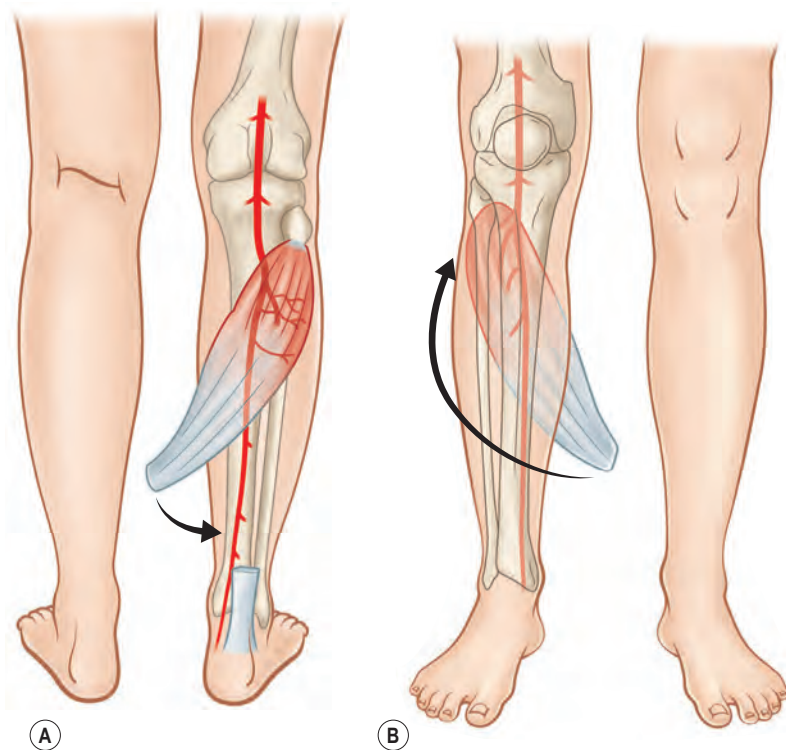


Fig. 22.68 Soleus flap. (A,B) Arc to middle third of leg.

3. Abductor digiti minimi

4. Lateral calcaneal artery flap.

Defects of the foot are most often due to trauma or the long-standing effects of underlying systemic disorders such as diabetes mellitus and peripheral vascular disease. These wounds can be extremely difficult to treat and often are best left uncovered until the underlying disease is treated (e.g., by revascularization). For some patients with severe, irreversible underlying systemic disease, local conservative wound care may be the only appropriate form of therapy.

When reconstruction is necessary, several issues must be addressed, such as the size of the defect and the patient's

vascular, neurosensory, and weight-bearing status. For small defects, skin grafts are often the procedure of choice provided that there is adequate protective soft tissue within the bed of the defect. For small defects involving weight-bearing areas, axial innervated skin flaps and fasciocutaneous flaps have been successful in providing stable coverage.^{143,337} For the deeper, more extensive foot defect, the use of a muscle or musculocutaneous flap is usually necessary. The local muscles available for use as flaps include the flexor digitorum brevis, the abductor hallucis, and the abductor digiti minimi. These muscles are small and are inadequate for larger defects. The use of a distant muscle (e.g., cross-foot flap) or microvascular free tissue transfer is usually necessary for coverage of any major wound (those with excessive size and depth or with component loss).

Mathes *et al.* demonstrated the anatomy of the flexor digitorum brevis for use as a flap in 1974.¹⁵ It is a type II muscle that measures approximately 10×4 cm. This muscle was then shown to be clinically useful to cover a calcaneal defect in 1974 by Vasconez *et al.*¹⁹ In 1980, Hartrampf *et al.* described a modification of this technique, using the muscle as an island flap that increased the arc of rotation. As an island flap based on the lateral plantar artery, the flexor digitorum brevis muscle reaches the malleolus and can cover the entire postero-superior aspect of the heel pad.³³⁸ The authors recommended that the patency of both the dorsalis pedis and the tibialis posterior artery should be confirmed before the lateral plantar artery is divided. In patients who have occlusion of either the dorsalis pedis or the tibialis posterior artery, the lateral plantar artery serves as a vital conduit of collateral flow and should not be divided for flap use. The flexor digitorum brevis, when transposed as a muscle flap, may provide stable coverage and is of benefit in both diabetic and nondiabetic patients (Fig. 22.72).^{339,340}

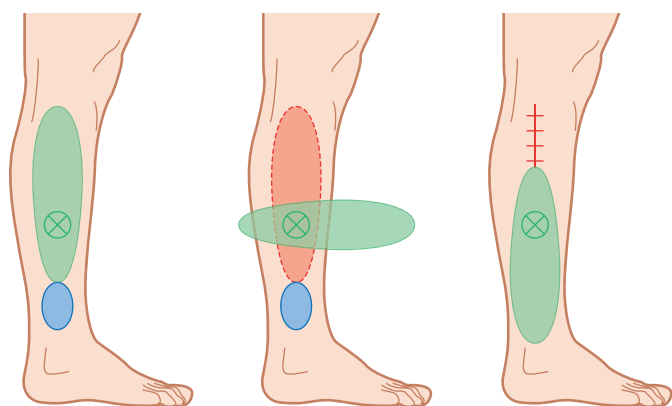


Fig. 22.69 The propeller flap based on a single perforator can be elevated as a fasciocutaneous or a skin flap harvested above the fascia. The flap is designed around a perforator as a pivot point and forming two blades with an unequal length that can be rotated to fill the defect.

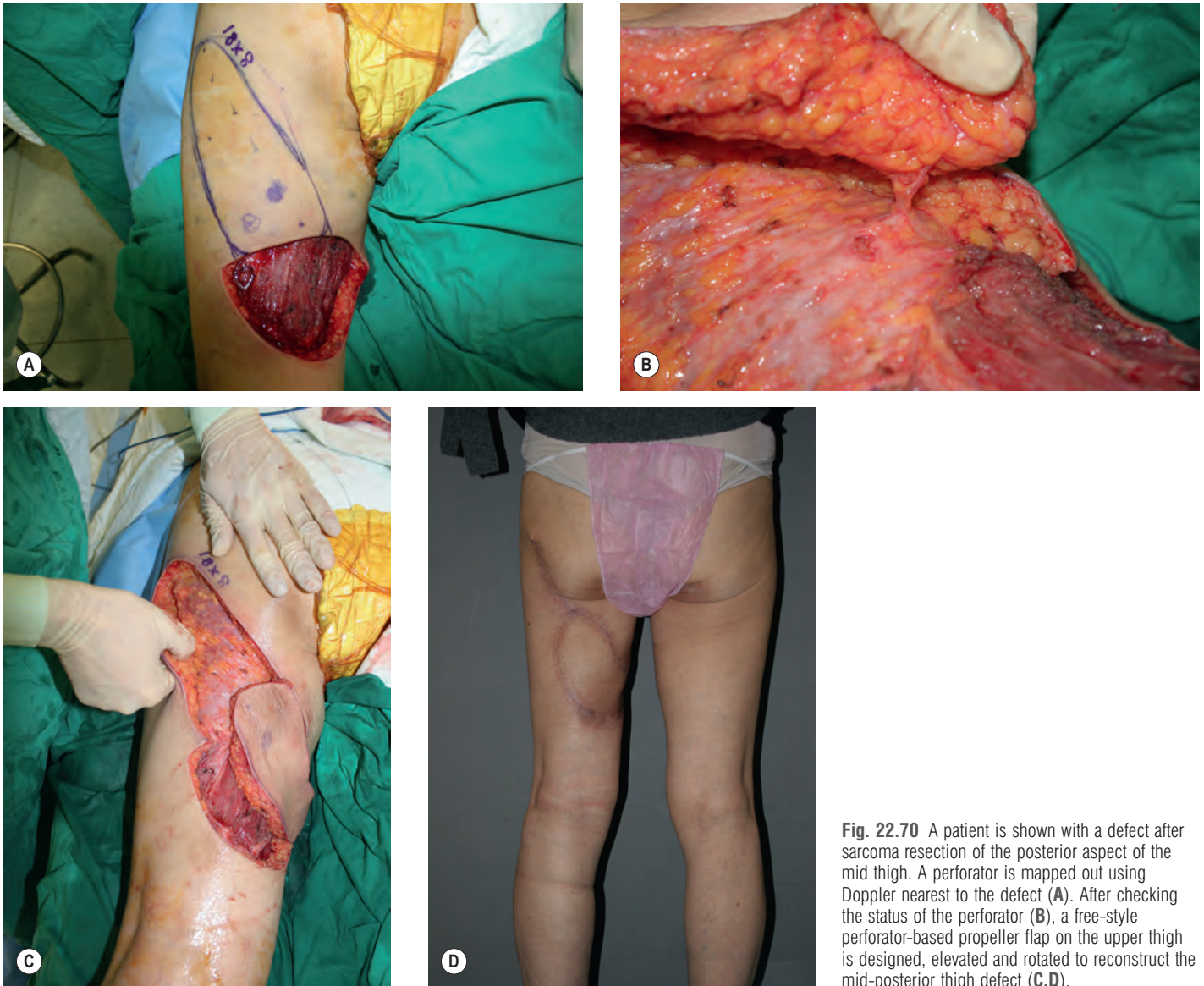


Fig. 22.70 A patient is shown with a defect after sarcoma resection of the posterior aspect of the mid thigh. A perforator is mapped out using Doppler nearest to the defect (A). After checking the status of the perforator (B), a free-style perforator-based propeller flap on the upper thigh is designed, elevated and rotated to reconstruct the mid-posterior thigh defect (C,D).

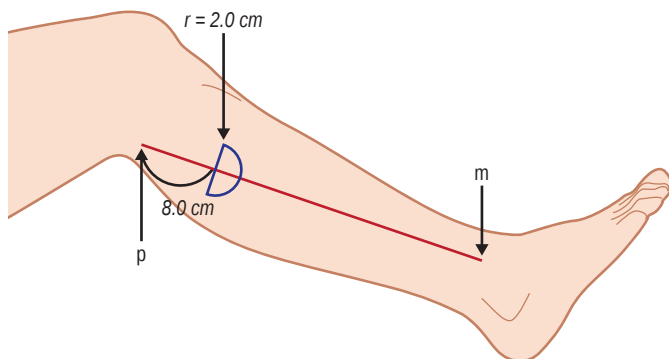


Fig. 22.71 The MSAP flap. The illustration shows that the first perforator is usually detected 8 cm from the midpoint of the popliteal crease within a distal half circle drawn with a 2 cm radius. m, medial malleolus; p, midline of popliteal crease. (Adapted from Kim HH, Jeong JH, Seul JH, Cho BC. New design and identification of the medial sural perforator flap: an anatomical study and its clinical applications. *Plast Reconstr Surg.* 2006;117:1609–1618.)

The retrograde lateral plantar artery flap was described by Reiffel and McCarthy in 1980.³⁴¹ The flap is fashioned by dividing the lateral plantar vessels proximally; the plantar fascia and the flexor digitorum brevis muscle can be elevated as a flap based on distal retrograde flow. This flap is particularly useful for coverage of medial and lateral metatarsal head defects.³⁴²

The abductor hallucis is a type II muscle with branches of the medial plantar artery as its dominant vascular supply.¹⁵ Based on this vascular pedicle the abductor hallucis can be elevated as a muscle or musculocutaneous flap, and it can reach defects just inferior to the medial malleolus as well as defects of the proximal medial aspect of the dorsum of the foot. Like the lateral plantar artery, the medial plantar artery should not be divided if either the dorsalis pedis or the posterior tibial artery is occluded. The abductor hallucis muscle flap may be distally based to reconstruct forefoot defects.³⁴³

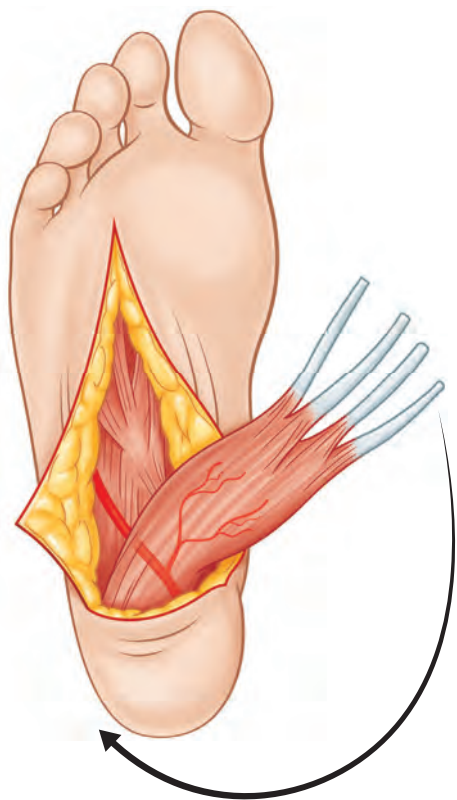


Fig. 22.72 Flexor digitorum brevis flap. Arc to heel.

The abductor digiti minimi is a type II muscle with branches of the lateral plantar artery as its dominant vascular pedicle.¹⁵ This small muscle based on its dominant pedicle can reach defects adjacent to the lateral malleolus. However, because of its size, the flap is limited in its ability to provide coverage of larger defects. In 1985, Yoshimura *et al.* reported the use of a distally based abductor digiti minimi muscle flap.³⁴⁴ This muscle flap based distally on the communication between the lateral plantar artery and the plantar arch can be used to cover small defects of the distal half of the foot. The abductor digiti minimi may be harvested with the lateral calcaneal artery sensate skin flap to cover plantar heel wounds.³⁴⁵

The lateral calcaneal artery is the terminal branch of the peroneal artery. The flap can be designed as a fasciocutaneous peninsula flap 4 cm wide extending from lateral malleolus to anterior Achilles tendon. The flap can extend vertically from lateral malleolus to the plantar surface of heel.^{346,347} After the transposition of the flap, the donor site frequently needs skin graft coverage.

Posterior trunk

Regional flaps:

1. Trapezius
2. Latissimus dorsi
3. Gluteus maximus
4. Scapular and parascapular
5. Paraspinous muscle.

Perforator flaps:

1. Intercostal artery perforators
2. Lumbar artery perforators.

The regional flaps used for reconstruction of midline and posterior trunk defects include three pairs of posterior trunk muscles: trapezius and latissimus dorsi muscle flaps for the upper and mid posterior trunk defects and the latissimus dorsi and gluteus maximus muscle turnover flap for the lower posterior trunk (Fig. 22.73). All three muscles have large cutaneous territories that allow them to be used as musculocutaneous flaps.³⁴⁸ In addition, other options include the scapular flap, parascapular flap, and the paraspinous muscle flap (Table 22.15). The selection for each of these regional muscle flaps must be made first by evaluating the defect and then selecting the relevant flap based on the understanding of the anatomy and the arc of rotation. These approaches may end up with too much tension and poor tissue vascularity of the flap that may be designed beyond the angiosome territory. In complex cases, it may require multiple flap or two-layered reconstruction resulting in increased risk of donor site morbidity.³⁴⁸ It can be critical for patients that may undergo radiation therapy to heal properly after the initial reconstruction. Although there are multiple muscle groups in the posterior trunk, reconstruction remains difficult using regional flaps.

The concept of perforators has allowed a new dimension in reconstructive surgery. It defines the vascular supply for a skin island from a single perforator penetrating the deep muscle fascia while sparing tissues surrounding the pedicle. The propeller flap intentionally rotates the flap based on a single perforator resulting in an effective transposition.^{59,60,349} By designing with accuracy, this perforator-based propeller flap can be used locally to cover various defects of the back without injuring muscle function, provides sufficient bulk to obliterate dead space, and can be closed primarily leading to minimal donor site morbidity (Fig. 22.74).¹⁸⁸ With the understanding that any perforator can be used as a flap, the free-style flap leads to flexible design of propeller flaps enhancing the chance for prompt reconstruction. The two major vascular systems of the back are from the intercostal artery and the lumbar artery perforators. According to the report by Saint-Cyr's group, in the lumbar region, two major areas of

Table 22.15 Regional flaps for posterior trunk midline defects	
Wound location	Muscle flap
Cervical	Trapezius muscle flap Latissimus dorsi flap
High thoracic Small defect Large defect	Trapezius muscle with split-thickness skin graft Latissimus with skin island Trapezius muscle (deep layer)
Thoracic Small defect Large defect	Latissimus advancement flap Reverse latissimus dorsi flap Paraspinous turnover flap Latissimus dorsi with skin island
Thoracolumbar and low lumbar	Latissimus dorsi with skin island Unipedicled latissimus Composite latissimus and gluteus maximus Paraspinous turnover flap

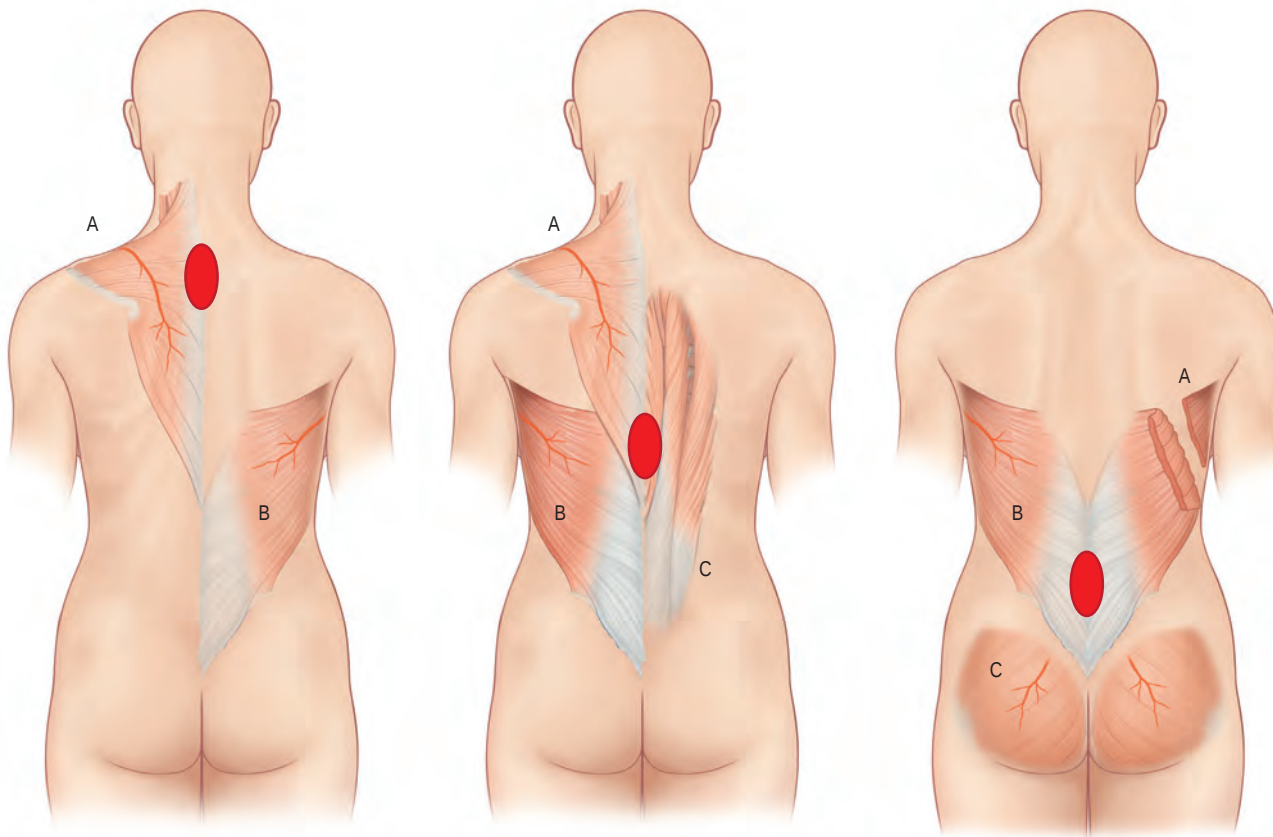


Fig. 22.73 (Left) The common flaps that can be used to reconstruct an upper thoracic cervical defect include (A) the trapezius muscle flap and (B) the latissimus dorsi flap. (Center) the common flaps that can be used to reconstruct a midthoracic defect include the (A) trapezius muscle flap, (B) latissimus dorsi flap, and (C) paraspinous turnover flap. (Right) Defects in the lower lumbar area can be reconstructed with (A) a reversal latissimus dorsi flap with skin island, (B) a composite latissimus and gluteus maximus flap, or (C) a superiorly based gluteus flap. (Adapted from Mathes DW, Thornton JF, Rohrich RJ. *Management of posterior trunk defects*. *Plast Reconstr Surg*. 2006;118:73e–83e.)

perforators are clustered within 10–20 cm of the coccyx and 10 cm from the midline. In the thoracic region, perforator location is clustered similarly distant from the midline at 10 cm, and 0–15 cm from C7.³⁵⁰ Any one of these perforators can be based as a perforator flap but the perforator with the strongest pulse and diameter may have a better flow to the skin flap and may be the preferable choice as pedicle.³⁵¹ Other sources can be perforators from the superior epigastric artery, deep inferior epigastric artery, superficial inferior epigastric artery, superior circumflex iliac artery, deep circumflex iliac artery and the superior gluteal artery.^{350,352} In cases where a large dead space is present, one can epithelialize the skin flap to obliterate it. Multiple perforator flaps can be elevated and rotated if the defect is too large for a single flap application.³⁵³

Pressure wounds

Regional flaps:

1. Gluteus maximus.

Distant flaps:

1. Tensor fascia lata
2. Gracilis
3. Hamstrings
4. Omentum.

Perforator flaps:

1. Sacral region:
 - Superior gluteal artery perforator (SGAP)
 - Inferior gluteal artery perforator (IGAP)
 - Lumbar artery perforator (LAP)
 - Parasacral artery perforator (PSAP)
 - Lateral intercostal artery perforator (LICAP)
2. Ischial region:
 - Inferior gluteal artery perforator (IGAP)
 - Adductor perforator
3. Trochanteric region:
 - Anterolateral thigh (ALT) perforator
 - Profunda femoris artery perforator (PFAP).

The gluteus maximus is a regional flap commonly used for the surgical treatment of pressure sores. It is a type III muscle and it is the flap of choice for reconstructing deep sacral and ischial pressure sores. Function-preserving techniques such as bilateral advancement flaps using only the superior halves of the gluteus maximus for sacral coverage are recommended for the ambulatory patient.^{49,354,355} Variations in technique, including the sliding gluteus maximus flap, the transposition gluteus maximus flap, and island flaps based on

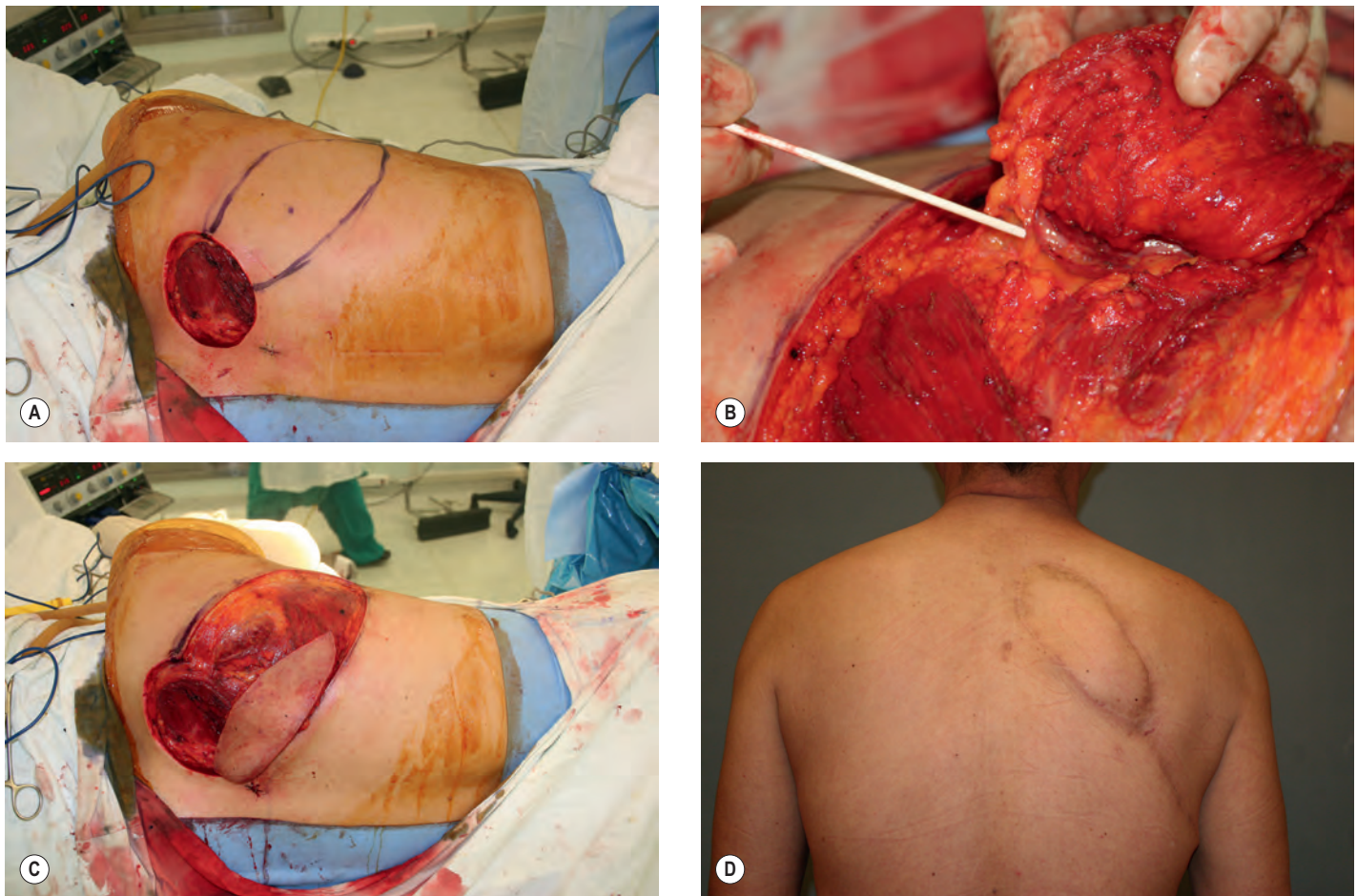


Fig. 22.74 Freestyle propeller flaps based on a single perforator with accurate design allows coverage of various defects of the back without injuring muscle function, provides sufficient bulk to obliterate dead space and can be closed primarily leading to minimal donor site morbidity. A patient with a defect of the upper back is shown (A). After identifying a perforator using Doppler, the design is completed to cover the defect and then elevated based on a single perforator (B,C). The patient is shown to have good contour and minimal donor site morbidity during follow-up (D).

musculocutaneous perforating vessels (muscle preserving) have been described.^{355–358} The sliding flap is indicated for small sacral defects, whereas the transposition flap (unilateral or bilateral) is generally appropriate for larger defects because it has a greater range of coverage. For extensive pressure sores, the gluteal thigh flap has also been useful.^{319,320,359,360}

More recently, the superior gluteal artery perforator flap has been used for the treatment of sacral pressure ulcers.³⁶¹ It affords the same skin as the gluteus maximus myocutaneous flap with the advantage that the muscle is completely spared and the pedicle length significantly increased. This is a particularly attractive alternative in the ambulatory patient.

Three distant muscles used in the reconstruction of pressure sores are the tensor fascia lata, gracilis, and the hamstrings. The tensor fascia lata (TFL) is a type I muscle that is useful for reconstructing trochanteric pressure sores.^{285,357,362} It is also a reliable alternative flap for ischial defects because of the following advantages: there is relatively low donor site morbidity, especially in an ambulatory patient; the flap provides vascularized, durable fascia; and the flap can provide sensibility in certain instances.

Several investigators have described the use of the innervated TFL flap, based on the lateral femoral cutaneous nerve (L2–L3), for reconstruction of ischial defects. They

have reported successful restoration of protective sensibility without recurrence of pressure ulceration in paraplegic patients with lesions below the L3 level.^{284,363,364}

The major disadvantage of the TFL flap is its relative thinness, a problem for the deeper pressure sore. In 1981, Schefflan described a technique to increase the bulk of the TFL flap. By de-epithelializing the distal aspect of the flap and folding the inferior portion of the flap underneath, part of the flap gains bulk. Used as a “sandwich”, the modified flap can usually fill the deeper defect.³⁶⁵ Modifications in the design of the TFL flap have been described in an attempt to minimize the donor site morbidity. Problems such as dog-ears, excessive tension at wound closure, skin necrosis at certain wound margins, and the need for skin grafts have prompted techniques such as the use of a bilobed TFL flap³⁶⁶ and the V–Y retroposition TFL flap.^{367,368} These modifications appear to facilitate donor closure in certain instances.

The gracilis is a type II muscle, first described in 1972 by Orticochea for use as a musculocutaneous flap.³⁶⁹ In the treatment of pressure sores, the gracilis is used primarily to repair the ischial defect.^{370,371} Use of the gracilis does not preclude the future use of the gluteus maximus or the posterior thigh flap if the ulcer recurs. The muscle can be elevated with the patient prone, but the distal muscle should be located before

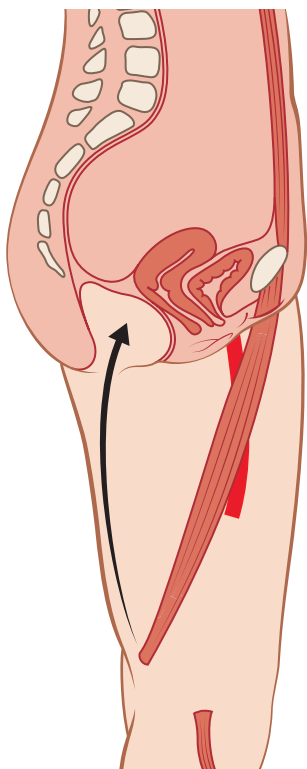


Fig. 22.75 Gracilis flap. Arc of rotation to the perineum.

the skin island is incised, in order to ensure the correct localization of the skin overlying the muscle (Figs. 22.75 & 22.76).

The gluteus maximus muscle (type III) is well situated for coverage of both sacral and ischial pressure sores. There are a number of modifications for its design and use for both ischial and sacral pressure sores. In general, it is preferable to use segmental transposition, reserving the superior half of the muscle based on the superior gluteal artery and associated venae comitantes for the sacral sore and the inferior half based on the inferior gluteal artery and associated venae comitantes for the ischial sore.

For the sacral sore, the cutaneous territory of the superior half of the muscle may be used as a V-Y advancement flap, or the skin island may be designed distally (near the muscle insertion) for use as a transposition flap or proximally (near the muscle origin) in V-Y advancement flap. For V-Y advancement flap, the superior half of the muscle's origin and insertion is divided so the composite of muscle plus the overlying soft tissue will cover the debridement site of the sacral decubitus. Although perforating vessels will allow bilateral V-Y advancement of the skin island with release of the muscle, adequate well-vascularized soft tissue and muscle are required to provide a long-lasting stable coverage over the sacrum (Figs. 22.77 & 22.78). When it is used as a transposition flap, the skin island and underlying muscle are transferred 180° to provide sacral coverage. It is not necessary to divide the superior muscle origin, although partial to complete release of the origin allows easier flap inset over the sacrum. As already mentioned, the SGAP flap has emerged as a useful alternative to the musculocutaneous flap.

The inferior half of the gluteus maximus is ideal for ischial sore coverage. The skin island is designed near the muscle



Fig. 22.76 (A–C) Gracilis musculocutaneous flap for ischial pressure sore coverage.

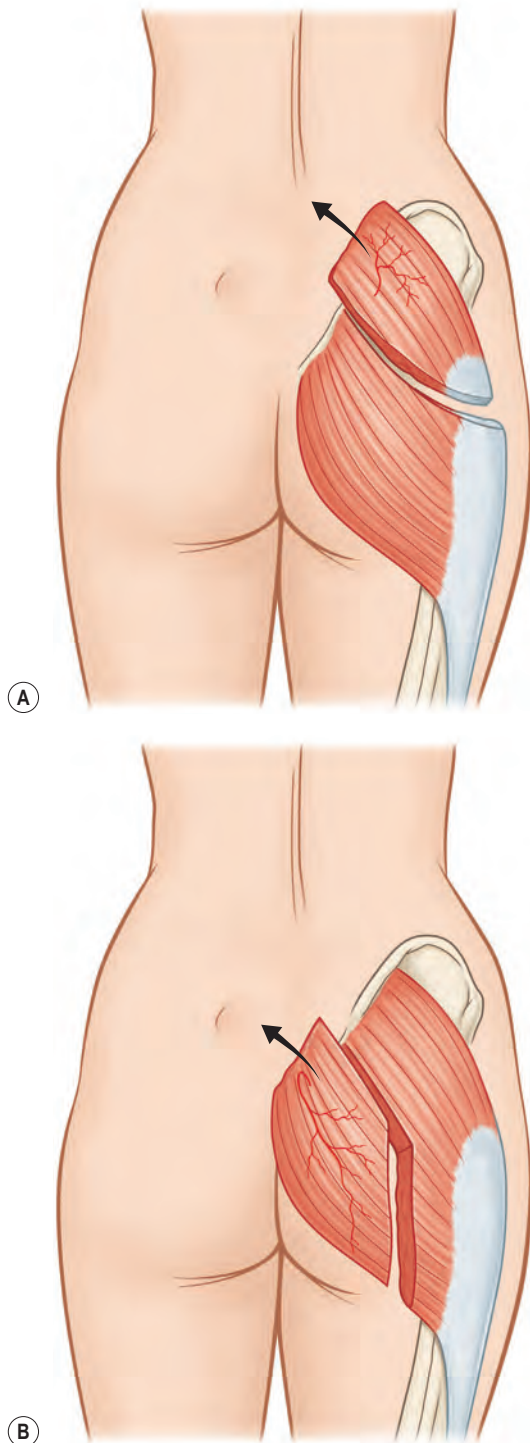


Fig. 22.77 Gluteus maximus–gluteal thigh flap. (A) V–Y segmental muscle advancement (superior half of gluteus maximus muscle). Flap advancement for sacral coverage. (B) V–Y segmental muscle advancement (inferior half of gluteus maximus muscle). Flap advancement for sacral coverage.

insertion. After splitting of the muscle, the muscle and overlying skin island are easily rotated 90° to the ischial defect. The condensed bulk of the muscle and its specific cutaneous territory provide stable coverage at the ischial site of reconstruction (Fig. 22.79; see also Fig. 22.9).

The hamstrings, consisting of the biceps femoris, semimembranosus and semitendinosus, are a group of muscles of

the posterior thigh. These muscles originate from the ischial tuberosity, although the biceps femoris also has a short head originating from the linea aspera of the femur. As a group, these muscles are useful in the reconstruction of ischial pressure sores. Used as a transposition flap, depending on the size of the defect, one or more of the hamstring muscles can provide ischial coverage. Hurteau *et al.* described V–Y advancement of the hamstring musculocutaneous flap for reliable coverage of the ischial pressure sore.³⁷² A triangular island of skin overlying the hamstring muscles is designed with the base of the triangle at the inferior margin of the ischial defect. The hamstring muscles are divided distal to the skin island, and the entire muscle group is mobilized superiorly. The origins of the hamstring muscles are detached from the ischium, thus enabling further advancement, and the flap is sutured into place. Long-term results reveal stable coverage of ischial pressure sores.³⁷³

The standard of muscle or musculocutaneous flaps to reconstruct the sores of the pelvic region is now being challenged by application of perforator or fasciocutaneous flaps.^{58,63,361,374–378} The use of perforator flaps for this region preserves the muscle function as it is spared during elevation, avoids a midline scar on the mid sacrum which can frequently break when using V–Y flaps, and enables the reconstruction of recurrent pressure sores as there are multiple perforators around the defect. Fig. 22.80 shows the angiosome of the buttock and the potential perforator flaps which can be used in this region.³⁷⁸

The GAP flap is based on either superior or inferior gluteal artery perforators. Using a hand-held Doppler or CT angiogram, one can identify potential perforators around the sacral defect (Fig. 22.81A). After the initial design of the flap based on the perforator, an incision should be made on one edge. Exploration for the perforator to the skin is performed either by a subfascial or superfascial approach. If there is no adequate perforator, one can always revert to using the flap as a simple rotation flap, hence the one-edge incision (Fig. 22.81B). After identifying the perforator, the final design should be made to completely cover the defect. Incision is then made for the rest of the margin and the perforator dissected. Once adequate length is secured, the skin or the fasciocutaneous flap based on the perforator can be easily rotated as a propeller to cover the defect and close the donor site primarily (Fig. 22.81C). If a single flap is not enough to cover the defect while achieving primary closure of the donor site, multiple flaps can be used to close the defect as well as achieve primary closure of the donor site. Similar approaches can be made for the lumbar artery perforator (LAP), parasacral artery perforator (PSAP), and lateral intercostal artery perforator (LICAP) flaps based on their perforator and the site of the defect.

The adductor perforator flap can be used as an island flap to cover a perineal defect or ischial sores. Due to its location, this perforator is frequently spared from previous surgeries and injuries. The cutaneous perforator of the adductor magnus muscle could be reliably found 8 cm distal to the groin crease and 2 cm posterior to the posterior border of the gracilis muscle. The pedicle length can be long as 8–9 cm, making it easy to reach the ischial sores.^{58,376} This flap can be bulky due to the excessive subcutaneous fat but can be debulked to fit the defect.

The posterior thigh, like the anterior, lateral and medial thigh, possesses rich perforators. The largest skin territory of

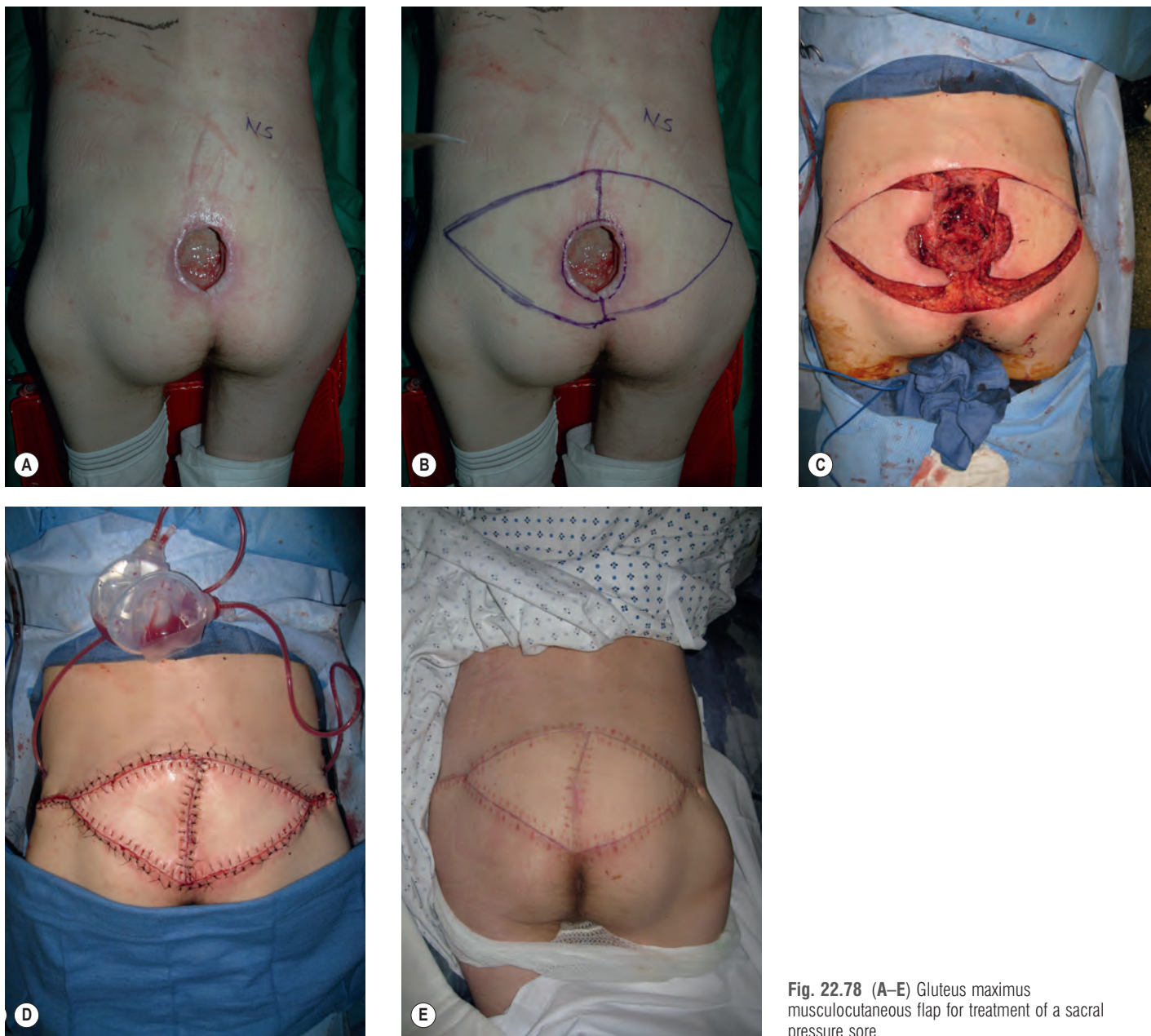


Fig. 22.78 (A–E) Gluteus maximus musculocutaneous flap for treatment of a sacral pressure sore.

the posterior thigh comes from the profunda femoris artery, especially the first and second perforating arteries out of the four.^{58,378–380} Any of the perforators can be potentially used as a regional flap to cover the trochanteric and ischial defects. These flaps are evolved from the fasciocutaneous flaps of the posterior thigh.^{320,359,381,382}

Microsurgical application of flaps

Basically all local flaps can be elevated on a pedicle as a free flap. The technique of microsurgery is critical along with the steps involved during the preoperative, intraoperative and postoperative period. These critical steps will be reviewed in other chapters. Most of the muscle and musculocutaneous flaps have been covered in the regional flap section. In this section, we will briefly review common perforator flaps that are used as free flaps.

Free perforator flaps

Anterolateral thigh (ALT)

The ALT flap remains as one of the most commonly used perforator flaps for reconstruction. The perforator is found in a relatively constant region and the pedicle can be long when harvested with the source vessel. It also can be used as a compound flap with the vastus lateralis muscle and the deep fascia can be used to reconstruct the tendon defects. It is widely used for head and neck reconstruction and extremity reconstruction.

A line is drawn between the anterior superior iliac spine and superior lateral border of the patella on the donor thigh. The perforator branches are identified with Doppler near the midpoint of this line. According to our clinical experience, about 90% of perforators are found within 3 cm diameter drawn at the midpoint of the line (Fig. 22.82).^{67,383–385} The skin



Fig. 22.79 (A–E) Inferior half of the gluteus maximus musculocutaneous flap for ischial coverage.

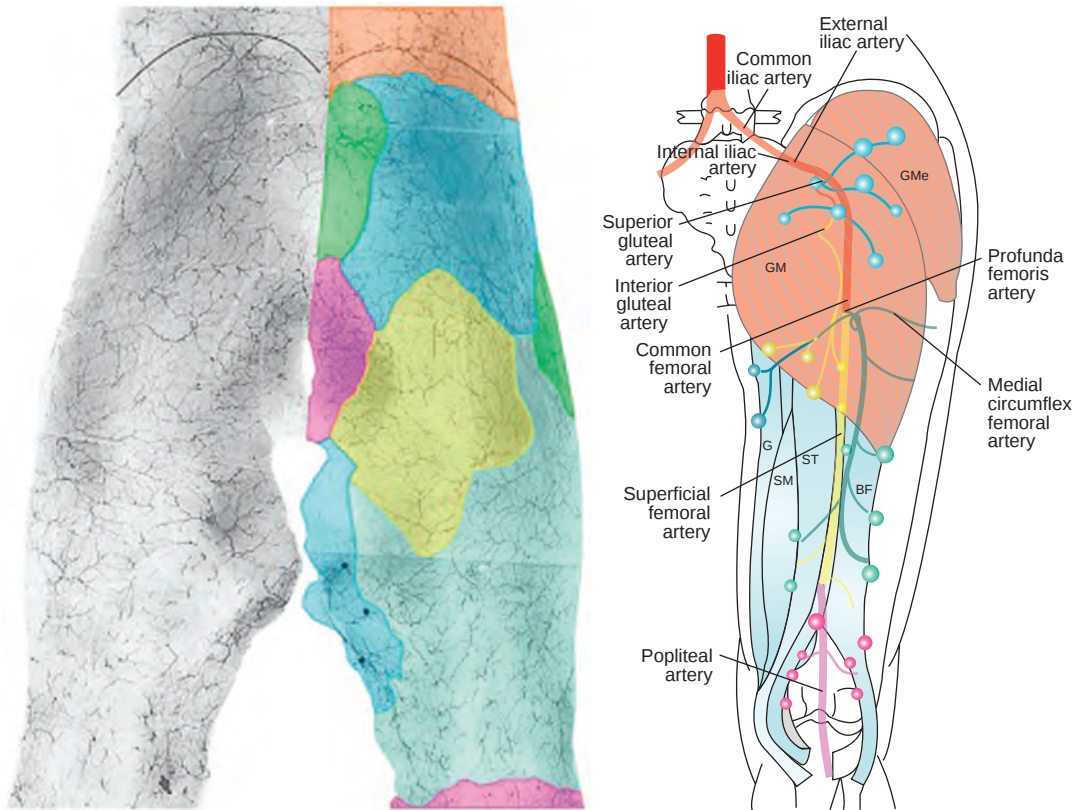


Fig. 22.80 Angiosome of the buttock and the potential perforator flaps which can be used in this region. Key: Orange, lumbar; top blue, superior gluteal; top green, lateral sacral; top purple, internal pudendal; yellow, inferior gluteal; lateral green, lateral circumflex femoral; lower blue, adductor; aqua, profunda; lower purple, source vessels. (Image from Pan WR, Taylor GI. The angiosomes of the thigh and buttock. *Plast Reconstr Surg.* 2009;123:236–249.)

flap is designed to include the perforator and is then elevated from the medial border of the flap. The incision is made through the deep fascia when elevated subfascially and raised until the intermuscular septum between the rectus femoris and vastus lateralis muscle is reached. At that point, the descending branch of the lateral femoral circumflex is explored along with the perforator to the skin flap (Fig. 22.83). The

pedicle length can be up to 20 cm, with maximal dimensions up to 40×20 cm.^{67,386} There have been some reports of variants where the dominant perforator to the ALT flap may originate from the transverse, oblique and ascending branch of the lateral circumflex femoral artery.³⁸⁷ Thus, a free-style elevation approach to accommodate these variations may be warranted.²⁷ The ALT flap is also an excellent local flap where it



Fig. 22.81 (A) A patient with a pressure sore. After identifying a perforator near the defect, in this case an inferior gluteal artery perforator, the rest of the flap is designed based on the free-style principle and then rotated to cover the defect (B,C).

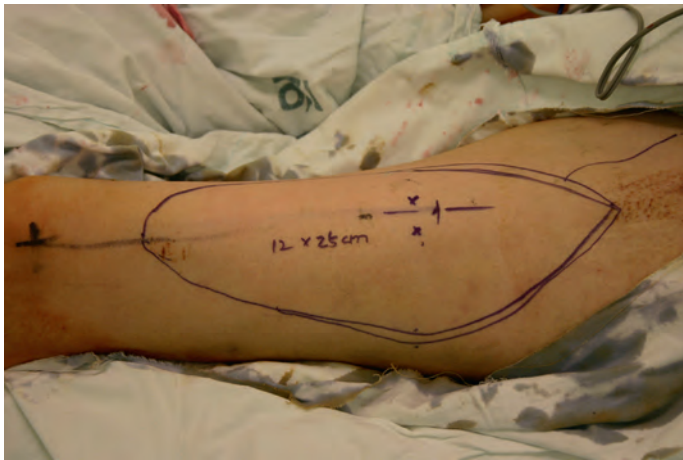


Fig. 22.82 A line is drawn between the anterior superior iliac spine and superior lateral border of the patella on the donor thigh. The perforator branches are identified with Doppler near the midpoint of this line. According to our clinical experience, about 90% of perforators are found within 3 cm diameter drawn at the midpoint of the line.

can reach the lower abdomen, pelvis, perineum and the knee by a reverse flow pattern.³⁸⁸ The flap can be harvested either as a perforator flap which includes only the perforator branch to the skin or as combined flap including the vastus lateralis muscle based on the descending branch of the lateral femoral circumflex system. The skin paddle can be defatted to about 5–8 mm thickness. The motor branch of the femoral nerve running medial to the descending branch of the lateral circumflex femoral artery should be preserved. To elevate as a sensate flap, a branch of the lateral femoral cutaneous nerve should be included. The donor site can be primarily closed depending on the laxity of the skin.

Deep inferior epigastric artery perforator (DIEAP) flap

The DIEAP flap evolved from the abdominal flaps as a free flap by Holmstrom and the pedicled flap by Hartrampf *et al.*^{223,389} Koshima and Soeda reported the first clinical use of the lower abdominal skin and fatty tissue for breast reconstruction without sacrificing rectus muscle and, since then, the use of perforator flaps for autologous breast reconstruction

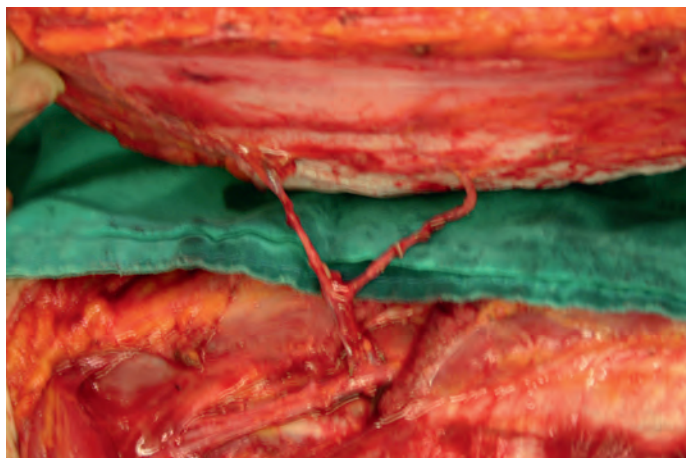


Fig. 22.83 Descending branch of the lateral femoral circumflex artery is explored along with the perforator to the skin flap.

has developed in an effort to perform a safe, reliable, reproducible reconstruction with low donor-site morbidity.^{53,55,56,64}

The DIEAP flap is now one of the first-line choices for autologous breast reconstruction. The deep inferior epigastric artery (DIEA) arises from the terminal aspect of the external iliac artery deep to the inguinal ligament then ascends from the lateral aspect of the rectus abdominis muscle toward the umbilicus. It ascends between the transversalis fascia and the peritoneum before penetrating the rectus abdominis muscle. The artery enters the middle third of the muscle most frequently (78%), with the lower (17%) and upper third (5%) less frequently.³⁹⁰ After penetrating the muscle, it gives off an average of five (plus or minus two) perforators supplying the skin. Most of the perforating vessels are found within 2 cm cranial and 6 cm caudal and between 1 and 6 cm around the lateral aspect of the umbilicus.^{58,391,392} The lateral perforators may be larger and easier to dissect, but the midline perforators supply better blood flow to zone III and to zone IV.

Preoperative planning consists of the flap design in which the proposed skin island should be centered over the identified perforators. Hand-held Doppler can be used to identify the perforators assisting the flap design. CT angiograms may help to choose the perforator with the best diameter and the least dissection of the muscular segment (Fig. 22.84).

The incisions are carried down to the abdominal fascia. Scarpa's fascia is carefully maintained, and beveling is performed at the lateral aspects and at the level below Scarpa's fascia only. Using electrocautery, the flap may quickly be raised at the suprafascial level to the lateral border of the anterior rectus fascia. When a perforator is encountered, the caliber and location of the vessels are assessed and if possible should be maintained until the largest perforator can be selected (Fig. 22.85).^{56,62} Then the dissection continues through the anterior rectus fascia and the rectus muscle reaching the source vessel (Fig. 22.86). Efforts should be made to minimize muscle and nerve injury if possible. Based on a single perforator, although this may vary between individuals, the flap dimension can reach 30–45 cm in width and 11–16 cm in

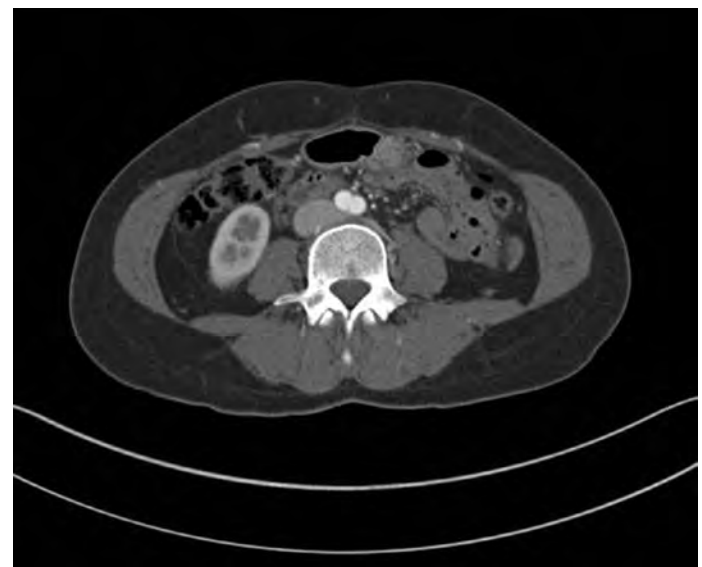


Fig. 22.84 CT angiograms may help to choose the perforator with the best diameter and the least dissection of the muscular segment.

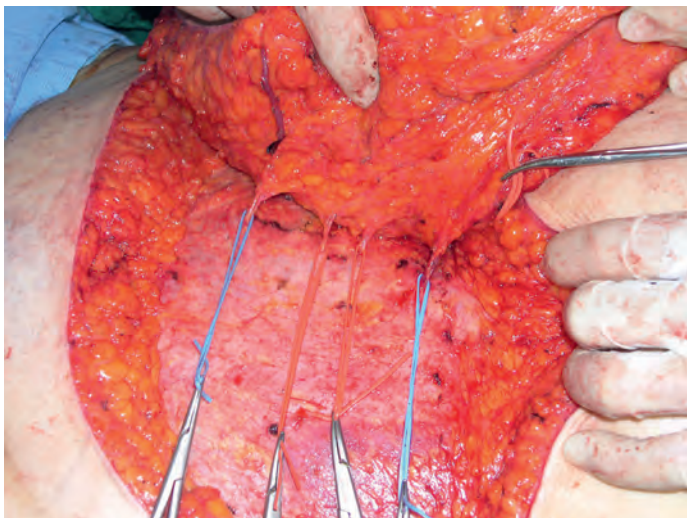


Fig. 22.85 When a perforator is encountered, the caliber and location of the vessels are assessed and if possible should be maintained until the largest perforator can be selected.

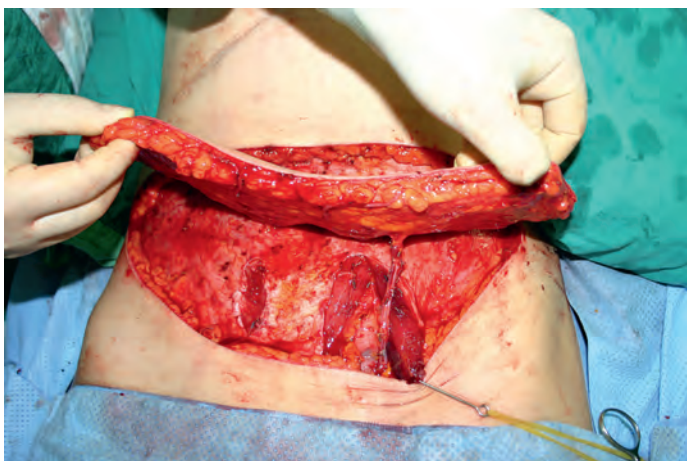


Fig. 22.86 The dissection continues through the anterior rectus fascia and the rectus muscle reaching the source vessel.

height.³⁹³ The donor site can be primarily closed depending on the laxity of the skin.

Thoracodorsal artery perforator (TDAP) flap

One of the most popular muscle flaps has been the latissimus dorsi muscle flap due to its constant vascular anatomy, big bulk of muscle and the ability to be harvested with a skin paddle. The same anatomy applies to the TDAP flap but without the need to sacrifice the muscle, thereby minimizing donor site morbidity and making it one of the workhorse perforator flaps.^{58,394} The flap can be harvested horizontally, longitudinally and in a bilobed shape but the dimension of the flap may be limited by the need for primary closure. This flap is commonly used for reconstruction of soft tissue.

The flap can be harvested in a supine position with the shoulder slightly supported by a pillow and the arm fixed in 90° abduction but the lateral decubitus position allows the flap to be harvested easily. Marking the anterior border of the latissimus dorsi muscle increases the possibility to include all

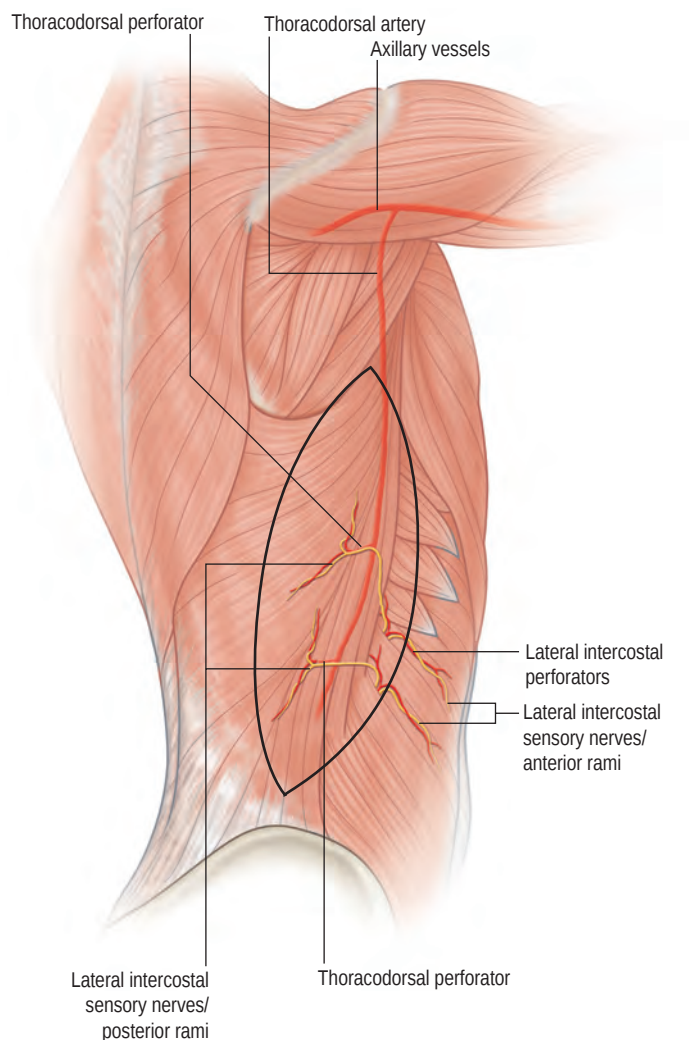


Fig. 22.87 Marking the anterior border of the latissimus dorsi muscle increases the possibility of including all perforators from this region. One can also use the Doppler to mark the perforators. Incision begins with the anteroinferior border of the skin paddle allowing identification of the anterior border of the latissimus dorsi muscle and adjustment of the flap design accordingly to place the anterior margin of the skin paddle in front of the anterior border.

perforators from this region. One can also use the Doppler to mark the perforators. Incision begins with the anteroinferior border of the skin paddle allowing identification of the anterior border of the latissimus dorsi muscle and adjustment of the flap design accordingly to place the anterior margin of the skin paddle in front of the anterior border. The main perforators overlies in the course of the descending branch of the thoracodorsal artery.³⁹⁵ After the perforator with the largest caliber and pulse, one can dissect the muscle toward the source vessel (Fig. 22.87). Pedicle length can be obtained up to 14–18 cm including the thoracodorsal vessels and skin dimensions can be up to 14×25 cm.^{58,396} The donor site can be primarily closed depending on the laxity of the skin.

Complications

Complications with the use of flaps fall into three categories: judgment, technique, and patient management. The most

common complications include seroma, hematoma, superficial skin necrosis, wound separation, inadequate coverage of the defect, infection, and partial or complete loss of the flap. By analyzing these complications in relation to judgment, technique, and patient management, the surgeon should be able to understand the cause of each complication in order to prevent subsequent complications.

Errors in surgical judgment are usually due to: inadequate preparation, inadequate flap design, or inadequate knowledge of anatomy.

Inadequate preparation is characterized by proceeding with a reconstructive procedure without having sufficient resources to perform the operation. For example, a surgeon may be asked to evaluate an elderly patient who has an extensive nonhealing ulcer involving the distal third of the leg. The surgeon recommends microvascular transplantation of a muscle flap, yet foregoes a preoperative arteriogram even though the patient has significant risk factors for peripheral vascular disease. Intraoperatively, adequate recipient vessels cannot be found and the flap is therefore aborted. This underscores the importance of preoperative preparation, especially if the diagnostic study directly impacts the surgical procedure planned.

Inadequate flap design is usually due to the surgeon's failure to account for every aspect of the surgical defect. The flap should not be designed and elevated prior to debridement of the wound. This may result in a significantly larger wound and an inadequately small flap. The flap should only be designed and elevated after the defect is completely debrided.

Inadequate knowledge of surgical anatomy may result in damage to the vascular pedicle during dissection, which can lead to failure of the flap. In addition to directly injuring the vascular pedicle, the surgeon can indirectly injure a pedicle by using a flap whose vascular pedicle is within the zone of injury, as in defects involving infection and radiation necrosis. Vascular pedicles within this environment may be compromised. For example, in a distally based flap, the minor pedicle is usually close to the defect and may be affected by the underlying cause of the defect. This is one reason that a distally based flap is less reliable than the muscle flap that is based on its dominant, major, or segmental secondary vascular pedicles. Through an appreciation of these subtle anatomic differences, proper flap selection and safe flap transposition can be achieved. It is imperative that the surgeon understand the precise anatomy of the muscle and musculocutaneous flap and the relationship to its vascular pedicle(s).

Surgical technique directly affects the outcome of any procedure. The handling of tissue, particularly vascular pedicles, is of utmost importance to the success of the flap. Vessels can be injured at any stage of the operation and are subject to spasm, kinking, shearing, and twisting. One preventative

measure is the placement of temporary sutures between the skin of the flap and the underlying muscle or fascia to prevent shearing of the musculocutaneous perforating vessels. Other techniques include avoidance of skeletonizing the vascular pedicle unless absolutely necessary to avoid spasm and injury. Lastly, in flaps that are tunneled beneath skin bridges, it is important to avoid a tourniquet effect produced by the potentially constrictive skin bridge.

Ultimate flap loss can be due to intrinsic or extrinsic reasons. Flap loss due to intrinsic reasons is largely caused by inadequate blood supply, which is the most common reason of flap compromise. Flap compromise due to extrinsic circumstances include infection, hypotension, and vasoconstricting agents such as pressors. Compression or tension on the flap due to hematoma is another extrinsic cause of flap compromise. Exploration of the flap should be expeditious when failure is suspected.

Donor site complications include fluid collections due to dead space (seroma, hematoma), wound separation, infection and injury to adjacent structures during flap harvest.

Errors in patient management are a common cause of postoperative complications. For patients undergoing flap surgery, the most common errors of management include: (1) inadequate attention to the patient's underlying medical conditions; (2) inadequate assessment or management of intravascular volume status; and (3) inadequate surveillance of flap viability and perfusion.

The safety and reliability of muscle and musculocutaneous flaps has been repeatedly demonstrated. Such successes now encourage surgeons to choose a more complex procedure than a simple one, especially if form and function can be improved. For example, in the reconstruction of a defect involving the lower leg, the soleus and gastrocnemius provide reliable and safe closure. However, the aesthetic and functional results may be unacceptable to certain patients. In these patients, a more sophisticated technique such as perforator-based propeller flaps, and perforator flaps with microsurgery approach may be appropriate and become the procedure of choice according to the reconstructive elevator concept.

Microvascular tissue transplantation is clearly indicated as the procedure of choice for certain defects. In fact, the use of microvascular free tissue transfer to reconstruct head and neck defects has revolutionized the field and has allowed both functional and aesthetically pleasing results for large extirpative defects. The term "microsurgery" has evolved to the concept of supermicrosurgery and the variety and concept of flaps are evolving from musculocutaneous to perforator flaps. Although the complexity of reconstruction and the approach are continuously evolving, the basic principle of flap selection and application remains the same: The quality of the result is far greater than the risk involved.



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Flap pathophysiology and pharmacology

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SYNOPSIS

- Introduction
- Pathophysiology of flap failure
- Surgical manipulation for augmentation of pedicle flap viability
- Pharmacological therapy for augmentation of pedicle flap viability
- Pharmacological therapy for augmentation of free flap viability
- Conclusion and future directions

BOX 23.1 Selected abbreviations

5HT ₂	serotonin
Ad.VEGF ₁₆₅	adenoviral vectors encoding the cDNA of VEGF ₁₆₅
ATP	adenosine triphosphate
EDCF ₅	endothelium-derived contracting factors
EDRF _s	endothelium-derived relaxing factors
ET-1	endothelin-1
FGF	fibroblast growth factor
MPO	myeloperoxidase
mPTP	mitochondrial permeability transitional pores
NADPH	neutrophilic nicotinamide adenine diphosphate
NE	norepinephrine
NHE-1	Na ⁺ /H ⁺ exchange isoform-1
NO	nitric oxide
O ₂ ⁻	superoxide radicals
•OH	cytotoxic hydroxyl radical
PDGF	platelet-derived growth factor
PGI ₂	prostacyclin
TRAM flaps	transverse rectus abdominis myocutaneous flaps
TXA ₂	thromboxane A ₂
VEGF	vascular endothelial growth factor

Introduction

Flaps, both pedicled and free, are routinely used to reconstruct defects resulting from injury, excision of tumors,

ulceration, or congenital malformation.¹⁻³ The clinical problem is that flap failure as a result of ischemic necrosis occurs in both pedicled and free flaps. In free flaps alone, ischemic necrosis occurs in 5–10% of patients, even in experienced hands.⁴⁻¹⁰ Flap necrosis can be partial or total.¹¹⁻¹³ Flap failure is time-consuming and costly because it requires repeated surgery and prolonged hospitalization. In the US, the additional operating room cost ranges from about \$40 000 to \$68 000 for each total free flap failure, and the additional surgeon reimbursement ranges from \$5000 to \$35 000 for each surgery.^{14,15} In addition, repeated surgery increases the incidence of donor site deformity and/or morbidity, with devastating effects on the patient. Therefore, we need to understand the pathophysiology of ischemic necrosis in pedicle and free flap surgery because this information may lead us to develop effective pharmacological therapies to prevent or salvage flap failure.

Pathophysiology of flap failure

Vasospasm and thrombosis in the pathogenesis of pedicle and free flap failure

Clinically and experimentally, ischemic necrosis occurs mainly in the distal portion of both pedicle and free flaps. The general consensus is that vasospasm and thrombosis due to surgical trauma and insufficient distal vascularity are the main pathogenic factors in pedicle and free flap failure,³ but little is known about the pathogenic mechanism. However, there are published reviews on the role of vasoactive neurohumoral substances in the local regulation of peripheral vascular tone in normal and diseased states.¹⁶⁻²¹ These articles may provide insight into the pathogenesis of vasospasm and thrombosis in flap surgery, as illustrated in Fig. 23.1. Briefly, endothelium-derived relaxing factors (EDRFs) such as prostacyclin (PGI₂) and nitric oxide (NO) cause relaxation of vascular smooth muscle and inhibit platelet aggregation.

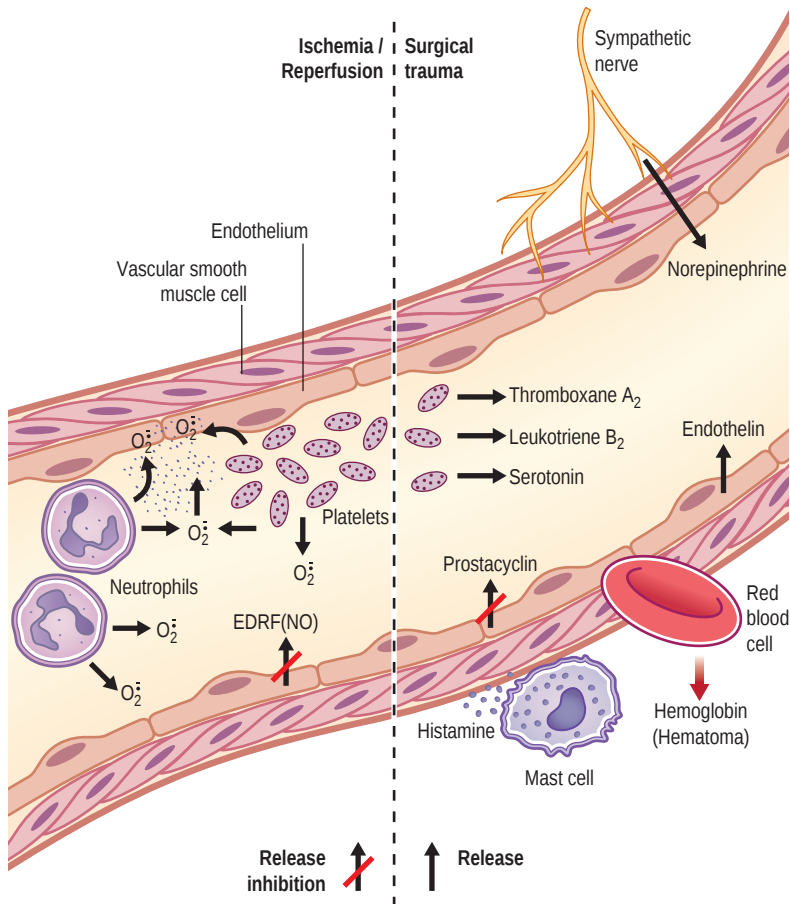


Fig. 23.1 Vasoconstriction in surgical trauma and vascular damage in ischemia–reperfusion injury. In surgical trauma, norepinephrine is released by sympathetic nerve endings and thromboxane A_2 , leukotriene B_4 , and serotonin are released by traumatized platelets and hemoglobin by red blood cells to cause vasoconstriction. Traumatized endothelial cells also decrease synthesis of vasodilating prostacyclin and endothelium-derived relaxing factor/nitric oxide (EDRF/NO). In reperfusion of ischemic blood vessels, superoxide radicals (O_2^-) are produced by platelets and neutrophils. These free radicals can damage blood vessels.

On the other hand, endothelium-derived contracting factors (EDCFs) such as thromboxane A_2 (TXA_2), and endothelin-1 (ET-1) raise vascular tone. Under physiological conditions, a balance of vascular effects between EDCFs and EDRFs maintains adequate tissue perfusion. However, an imbalance can occur as a result of surgical trauma, as shown in Fig. 23.1. Specifically, traumatized sympathetic nerve endings release norepinephrine (NE), causing vasoconstriction and platelet aggregation. The NE released by the sympathetic nerve endings, leukotriene B_4 , serotonin ($5HT_2$) and TXA_2 released by the platelets, and the ET-1 released by the traumatized vascular endothelial cells can cause vasoconstriction and intravascular platelet aggregation, especially in the small arteries in the distal portion of the flap where the perfusion pressure is low and the concentration of these vasoconstrictive substances is high due to the downstream effect. Hemoglobin from hemolyzed red blood cells (e.g., hematoma) is also a potent vasoconstrictor. The histamine released by the mast cells changes the membrane permeability, resulting in edema formation. Furthermore, the synthesis and release of EDRFs such as PGI_2 and NO from the traumatized vascular endothelium are depressed. In addition, the rate of endothelial degradation of NE and $5HT_2$ by catechol-O-methyl transferase and monoamine oxidase, respectively, is reduced in situations of impaired endothelial function. The end result is that there are high local levels of vasoconstrictive and prothrombotic neurohumoral substances in surgical trauma and these

substances exacerbate vasospasm and promote thrombosis in flap surgery.

In reperfusion of ischemic blood vessels, superoxide radicals (O_2^-) are produced by platelets, neutrophils, and endothelial cells and these free radicals can damage vascular walls during reperfusion (see Fig. 23.1).

Xanthine dehydrogenase/xanthine oxidase enzyme system in pathogenesis of ischemia–reperfusion injury in free flap surgery

In free flap surgery, skin and muscle are subjected to warm (room-temperature) global ischemia under vascular clamp control during transfer from donor site to recipient site prior to re-anastomosis. Human muscle and skin can withstand 2–2.5 hours and 6–8 hours of warm global ischemia, respectively.^{22–26} Excessive ischemic insult can result in ischemia–reperfusion injury caused by energy depletion and formation of oxygen-derived free radicals, as shown in Fig. 23.2. During prolonged ischemia, adenosine triphosphate (ATP) in skin and muscle is catabolized stepwise to hypoxanthine, with concomitant increase in cytosolic Ca^{2+} .²⁷ At the same time, a cytosolic protease is activated by intracellular Ca^{2+} and it converts xanthine dehydrogenase to xanthine oxidase.^{28,29} During reperfusion, the xanthine oxidase generates superoxide (O_2^-) by univalent reduction of

Tissue ischemia
(ATP catabolism)

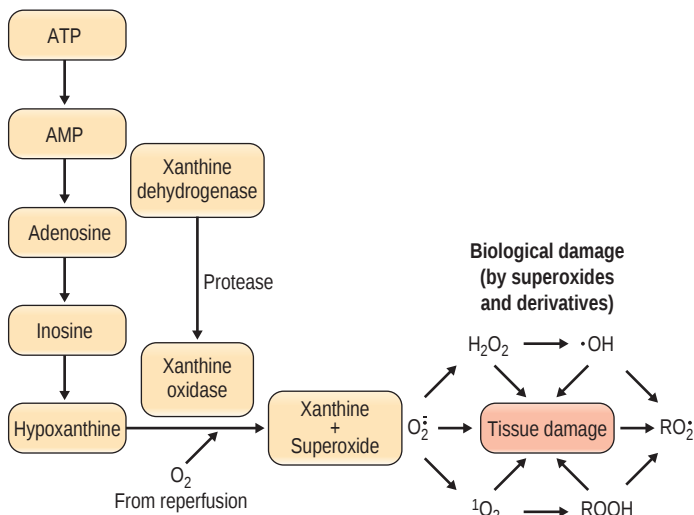


Fig. 23.2 Pathogenesis of oxygen-derived free radicals in reperfusion of ischemic tissues. AMP, adenosine monophosphate; ATP, adenosine triphosphate; $O_2^{\cdot -}$, superoxide; H_2O_2 , hydrogen peroxide; $\cdot OH$, hydroxyl radical; 1O_2 , singlet oxygen; $RO_2^{\cdot}$, peroxy radicals; $ROOH$, hydroperoxide.

molecular oxygen in the presence of hypoxanthine.³⁰ The unstable $O_2^{\cdot -}$ forms H_2O_2 spontaneously by dismutation. Furthermore, the unstable $O_2^{\cdot -}$ also interacts with H_2O_2 in the presence of a transition metal (e.g., iron) to form the most potent cytotoxic hydroxyl radical ($\cdot OH$) through the Haber-Weiss (Fenton) reaction,³¹ as shown in Fig. 23.2. There is evidence to suggest that this hypoxanthine/xanthine oxidase system is a main source of oxyradicals in ischemic rat skin and muscle.^{32,33} Furthermore, inhibition of xanthine oxidase activity by allopurinol and depletion of xanthine oxidase with a tungsten diet have been shown to attenuate the microvascular damage in rat skeletal muscle subjected to 2 hours of ischemia and 30 minutes of reperfusion.³⁴

However, there is also evidence to indicate that the hypoxanthine/xanthine oxidase system is not a main source of oxyradicals in pig and human skin and skeletal muscle. Control pig and human skin samples have been found to contain minimal xanthine oxidase activity, almost 40 times less than that of the rat, and xanthine oxidase activity did not rise during the first 8 hours of ischemia in these experiments.³⁵ In pigs, intravenous allopurinol given 60 minutes before ischemia did not protect cutaneous or musculocutaneous flaps from necrosis when subsequently subjected to 8 hours of warm ischemia and 5 days of reperfusion.³⁶ Similarly, we observed that xanthine oxidase activity in pig and human skeletal muscle was minute (<0.5 mU/g wet weight) compared with that of the rat.³⁷ In addition, we observed that 5 days of competitive xanthine oxidase inhibitor treatment (allopurinol 25 mg/kg i.v., b.i.d.) starting 2 days before ischemia or 3 days of noncompetitive xanthine oxidase inhibitor treatment (oxypurinol, 25 mg/kg, i.v., b.i.d.) starting 15 minutes before reperfusion did not attenuate pig latissimus dorsi muscle necrosis when subjected to 5 hours of ischemia and 48 hours of reperfusion.³⁷

Neutrophilic nicotinamide adenine diphosphate (NADPH) and myeloperoxidase (MPO) enzyme system in pathogenesis of ischemia/reperfusion injury in free flap surgery

There is accumulated evidence to indicate that neutrophils may play an important role in ischemia-reperfusion injury in free flap surgery. For example, it is well known that activated neutrophils produce large amounts of $O_2^{\cdot -}$ via NADPH oxidase, and these $O_2^{\cdot -}$ dismutates yield a high concentration of H_2O_2 and $\cdot OH$, causing tissue damage.³⁸ MPO, which is unique and abundant in neutrophils, catalyzes the conversion of H_2O_2 to hypochlorous acid ($HOCl$), a potent cytotoxic oxidizing agent ($H_2O_2 + Cl^- + H^+ \rightarrow HOCl + H_2O$).^{39,40} Furthermore, it was reported that treatment with monoclonal antibodies against neutrophil-endothelium adhesion molecules attenuated ischemia-reperfusion-induced skin necrosis in rabbit ears,⁴¹ rat epigastric island skin flaps,⁴² and skin and muscle in pig latissimus dorsi musculocutaneous flaps.⁴³ Treatment with monoclonal antibody against neutrophil-endothelium adhesion molecules also attenuated arteriolar vasoconstriction induced by ischemia-reperfusion injury.⁴⁴ Finally, neutrophil depletion ($\sim 95\%$) with mechlorethamine significantly reduced necrosis in pig latissimus dorsi muscle flaps subjected to 5 hours of warm ischemia and 48 hours of reperfusion.³⁷ Also, neutrophil depletion attenuated vascular injury in dog gracilis muscle subjected to 4 hours of warm ischemia and 1 hour of reperfusion.⁴⁵

Paradoxically, there are arguments against the important role of neutrophils in the pathogenesis of animal or human myocardial ischemia-reperfusion injury.⁴⁶⁻⁴⁸ Several investigators found that ischemia-reperfusion injury could be induced in neutrophil-free systems such as in cultured animal cardiomyocytes⁴⁹ and human atrial strips^{50,51} and in isolated perfused animal hearts.⁵²⁻⁵⁴ In clinical studies, free oxyradical scavengers were not effective in protecting myocardium from ischemia-reperfusion injury.^{55,56} Furthermore, although monoclonal antibody to intercellular adhesion molecule-1 and anti-CD18 antibodies were effective in protecting myocardium against ischemia-reperfusion in laboratory animals,^{57,58} clinical trials with these agents yielded negative results.⁵⁹⁻⁶¹ More recently, we observed that ischemia-reperfusion injury was also induced in human rectus abdominis muscle strips cultured in neutrophil-free buffer.⁶² There is the possibility of species difference in the role of neutrophils in the pathogenesis of ischemia-reperfusion injury. Therefore, it is important to clarify the causal role of neutrophils in ischemia-reperfusion injury in human skin and skeletal muscle.

Intracellular Ca^{2+} overload in pathogenesis of ischemia-reperfusion injury in free flap failure

Recently, experimental evidence has shown that intracellular Ca^{2+} overload plays a key role in causing cell death during myocardial reperfusion.⁶³ The pathogenic mechanism is summarized in Fig. 23.3. It appears that, in sustained ischemia, mitochondrial ATP synthesis ceases and glycolysis ensues, resulting in a net breakdown of ATP and an accumulation of

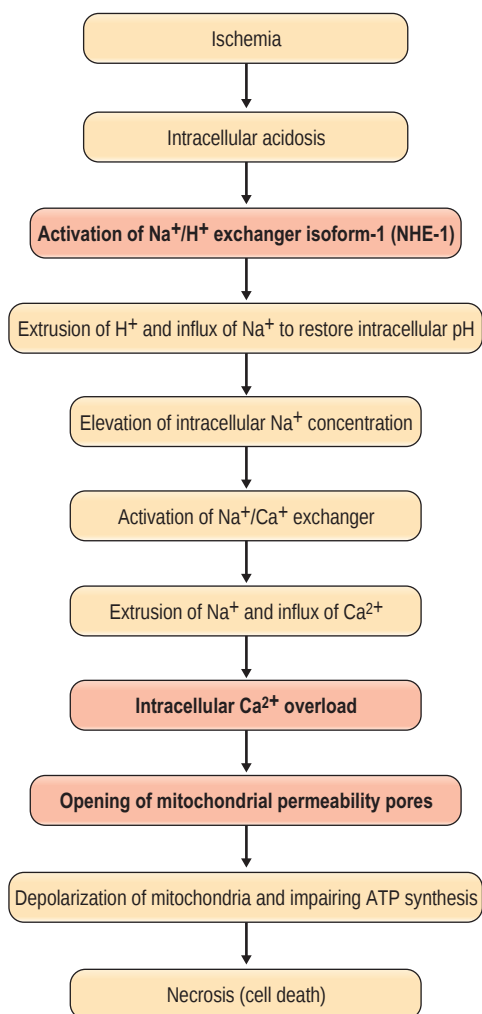


Fig. 23.3 Proposed role of intracellular Ca²⁺ overload in the pathogenesis of ischemia-reperfusion injury. ATP, adenosine triphosphate.

lactate and intracellular H⁺,⁶⁴ causing intracellular acidosis. This build-up of intracellular H⁺ activates the Na⁺/H⁺ exchanger isoform-1 (NHE-1) antiporter, resulting in extrusion of H⁺ and accumulation of intracellular Na⁺ to restore intracellular pH. There is a further increase in intracellular Na⁺ accumulation because Na⁺ extrusion is limited by inactivation of the energy-dependent Na⁺-K⁺-ATPase pump.^{65,66} Elevation of intracellular Na⁺ concentration causes an increase in intracellular Ca²⁺ by activation of the Na⁺/Ca²⁺ exchanger causing Ca²⁺ influx.^{65,67–70} If these events continue, the cytosolic Ca²⁺ will be overloaded, and significant uptake of Ca²⁺ from the cytosol to the mitochondria will occur, resulting in mitochondrial Ca²⁺ overload⁷¹ which causes depolarization of mitochondria and impairs ATP synthesis, resulting in cell necrosis⁵² (see Fig. 23.3). However, the NHE-1 may be inhibited⁷² if the extracellular acidosis is more pronounced than the intracellular acidosis after a prolonged period of ischemia.⁷³ At reperfusion, the rapid washout of the extracellular H⁺ reactivates the NHE-1, resulting in further extrusion of intracellular H⁺, and further accumulation of intracellular Na⁺, causing further cytosolic Ca²⁺ overload through Na⁺/Ca²⁺ exchange.^{67,74} Again, cytosolic Ca²⁺ overload causes mitochondrial Ca²⁺ overload, impairing ATP synthesis and resulting in cell

death.^{52,71} Recently, we have seen evidence to suggest that mitochondrial Ca²⁺ overload plays an important role in ischemia-reperfusion in skeletal muscle and this will be discussed later, along with the therapeutic treatment aimed at preventing mitochondrial Ca²⁺ overload.

Pathogenesis of no-reflow phenomenon in free flap surgery

May *et al.* used rabbit island epigastric skin free flaps to study the pathogenesis of the no-reflow phenomenon in free flap surgery.⁷⁵ They observed that ischemia induced swelling of the endothelial and parenchymal cell, narrowing of the capillary lumen, which led to intravascular aggregation of blood cells, and leakage of intravascular fluid into the interstitial space to form edema. This pathology increased with the increase in length of ischemic time from 1 to 8 hours and the obstruction of blood flow reached a point of irreversibility after 12 hours of ischemia, leading to no reflow and ultimate death of the flap. Three pathogenic mechanisms have been suggested to play a central role in the development of the no-reflow phenomenon in the skeletal muscle of laboratory animals: (1) oxygen-derived free radicals causing damage in the endothelial and parenchymal cells; (2) this cell membrane damage allowing Ca²⁺ influx, resulting in intracellular overload; and (3) change in arachidonic acid metabolism resulting in synthesis of less vasodilating and antithrombotic PGI₂ by the endothelium and increased synthesis of vasoconstricting and thrombotic TXA₂ by platelets.⁷⁶

Surgical manipulation for augmentation of pedicle flap viability

Clinically and experimentally, there are several surgical manipulations which have proved effective in augmenting flap viability.

Flap design in augmentation of pedicle flap viability

One of the misleading principles in plastic surgery is that the viable length of a skin flap depends on the width of the pedicle. Milton was the first to disprove this principle.^{1,77–79} Using a random-pattern skin flap model in the pig, it was demonstrated that the ultimate surviving length of a pedicle flap is determined by the balance between perfusion pressure and vascular resistance. Increasing the width of pedicle flaps merely adds additional vessels of the same type and the same perfusion pressure and thus cannot increase the length of flap viability (Fig. 23.4). However, in other locations of the body, increasing the width of the pedicle may increase the chance of including a large artery. Therefore, one of the surgical manipulations to augment flap viability is the conversion of a random-pattern skin flap to an arterialized or axial skin flap by incorporating a direct artery or a larger perforator.

Surgical delay in augmentation of pedicle flap viability

Surgical delay and vascular delay are proven techniques for augmenting flap viability in human patients,^{80–84} as well as in

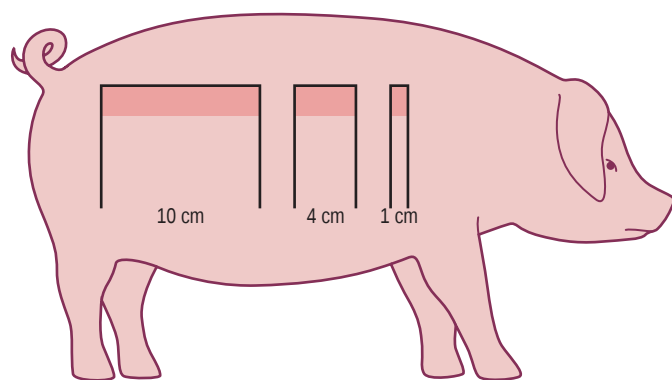


Fig. 23.4 The length-to-width ratio concept in flap design.

laboratory animals such as mice, rats, rabbits, and pigs.^{85–98} It takes two to three stages in surgical delay of pedicle skin flaps in order to augment flap viability. Specifically, a skin flap is mapped out on the donor site and incised on its two longitudinal sides. The flap is then undermined to form a bipedicle flap and is sutured back to the donor site. Two to three weeks after construction of the bipedicle flap, the third side (distal end) is cut in one or two stages at 2–3 days apart. At the end of this stage, a single pedicle flap is completely raised and the distal portion of the flap is moved to the recipient site for wound coverage without skin necrosis.^{1,99} In studies with pig random-pattern skin flaps, we and other investigators showed that surgical delay increased skin flap capillary blood flow between 2 and 7 days of delay.^{100,101} This increase in capillary blood flow was mainly in the distal random portion of the delayed skin flaps.¹⁰¹

Vascular delay in augmentation of pedicle flap viability

In mice, rats, and rabbits, vascular delay for augmenting blood flow and viability in the distal portion of latissimus dorsi muscle flaps was achieved by dividing distal perforating arteries at 1–2 weeks prior to raising the muscle flaps.^{93,95,96} This phenomenon was also achieved in transverse rectus abdominis myocutaneous (TRAM) flaps in laboratory animals as well as in human patients. Division of perforators or one or two dominant arteries that supply blood to the rectus abdominis muscle 2–3 weeks before flap surgery significantly augmented viability in TRAM flaps in rats^{91,92,94,97} and augmented skin and muscle blood flow and viability in TRAM flaps in pigs.^{91,92} In human patients, ligation of the deep inferior epigastric arteries 2–4 weeks before flap surgery augmented skin blood supply^{83,102,103} and viability in TRAM flaps.^{80–82,84}

Surgical and vascular delay have been proven clinically effective in augmenting flap viability, but these surgical procedures are costly and time-consuming. They require at least one additional surgical step done under general anesthesia. Vascular delay by embolization does not require general anesthesia, but it requires local anesthesia and catheterization performed in the interventional radiology department.¹⁰⁴ Recently, “recharging” of the TRAM flap has been described as an alternative technique to augment flap perfusion.¹⁰⁵ The evolution of microsurgery saw the development of free flaps. The idea was to improve flap blood flow and viability. TRAM

free flaps are a good example as the free TRAM is perfused by the more dominant deep inferior epigastric pedicle rather than the less dominant superior epigastric vessels that supply the pedicled TRAM.^{105–110} However, in some situations free flap surgery is not available. It requires specialized microsurgical staff and equipment and long operating room time. Furthermore, free flap surgery is not without morbidity and flap ischemic necrosis due to thrombosis and vasospasm occurs in 5–10% of patients.^{4–10,110} Therefore, there is the need to understand the mechanism of the surgical delay phenomenon through research to identify pharmacological strategies to prevent/treat ischemic necrosis.

Mechanism of surgical delay in augmentation of pedicle flap viability

Many investigators have studied the surgical delay phenomenon in laboratory animals in order to gain insight into the pathogenesis and pharmacological treatment for skin flap ischemic necrosis. Several hypotheses have emerged from these studies.

Surgical delay procedure reduces arteriovenous (AV) shunt flow

Reinisch reported good correlation between postoperative fluorescein staining and the eventual skin viability in pig skin flaps. He detected warm skin temperature beyond the fluorescein dye marker in the distal portion of the pig skin flap.¹¹¹ He also demonstrated ⁵¹Cr-labeled red blood cells and technetium and ⁸⁵Sr-microsphere (15 μm) activity beyond the fluorescein dye staining in acute pig skin flaps.¹¹¹ Taken together, he hypothesized that, in acute skin flap surgery, distal ischemic necrosis was caused by opening of AV shunt flow as a result of sympathetic denervation. He speculated that shunt flow occurred throughout the skin flap and the flow in the proximal areas is sufficient to supply both the AV and capillary (nutrient) blood flow, but the shunting became lethal in the distal areas of the skin flap where the total blood flow was low. In surgical delay, the bipedicle skin flap provided sufficient blood supply during the early period of sympathetic denervation and opening of AV shunts. Pearl presented data from rat abdominal arterial skin flaps, which supported Reinisch’s hypothesis, and also suggested that surgical delay allowed the skin flap to recover from its hyperadrenergic state before converting the bipedicle to single-pedicle skin flaps.¹¹² However, these observations were not supported by other investigators. For example, Prather *et al.*, using various laboratory techniques (fluorescein dye test, xenon clearance, angiography, ⁵¹Cr-tagged red blood cells and thermometry), failed to detect any evidence of vascular perfusion in the non-fluorescein distal portion of acute axial pattern skin flaps in the pig.¹¹³ In contrast to Palmer’s findings¹¹⁴ in rat dorsal skin flaps, Cutting *et al.*^{115,116} did not observe persistent adrenergic denervation in delayed bipedicle skin flaps. Later, Guba used 15 μm and 50 μm radioactive microspheres to measure capillary (nutrient) and total blood flow, respectively, and to calculate AV shunt flow in bipedicle axial pattern pig skin flaps. Both capillary and AV shunt flow increased between 2 and 7 days of delay in pig bipedicle skin flaps, but this increase in capillary blood flow in delayed bipedicle skin flaps was not the result of a decrease in AV shunt flow.¹⁰⁰

Subsequently, using 15 μm and 50 μm radioactive microspheres as well as fluorescein dye, Kerrigan¹¹⁷ found no evidence of AV shunt flow in the distal portion of acute random and arterial pig skin flaps destined to necrose, as indicated by lack of fluorescein penetration. Finally, using a similar radioactive microsphere technique, Pang *et al.* demonstrated that AV shunts played no important role in the pathogenesis of distal ischemic necrosis in random-pattern skin flaps in the pig and augmenting distal skin viability by surgical delay did not rely on closing of AV shunts, but vasodilation of existing blood vessels.^{101,118} It is important to point out that there may also be species differences in the extent of AV shunt flow in the skin assessed by the radioactive microsphere technique. Specifically, our lab observed in the pig that the AV shunt flow in the control skin and in the skin of acute and delayed random-pattern skin flaps within 6 hours postoperatively was ~60% of the total blood flow.¹⁰¹ However, Sasaki and Pang¹¹⁹ observed in the rat that the AV shunt flow in abdominal island skin flaps within 6 hours postoperatively was ~10% of the total skin blood flow. More recently, Kreidstein *et al.*¹²⁰ in our laboratory observed that the AV shunt flow in isolated perfused human para-umbilical skin was ~1%. Taken together, these studies seem to indicate that AV shunt flow does not play an important role in the pathogenesis of distal ischemic necrosis in acute pedicle skin flaps.

Surgical delay procedure depletes vasoconstriction and prothrombotic substances in the skin flap

Local tissue content of vasoconstricting and prothrombotic substances such as NE, TXA₂, 5HT and ET-1 are known to be elevated by surgical trauma.^{3,121–135} These substances are released locally by traumatized blood cells, endothelial cells, and sympathetic nerve endings (see Fig. 23.1). These are potent vasoconstrictors in skin vasculature.^{134,136–143} There is a general consensus that vasospasm and thrombosis play an important role in the pathogenesis of ischemic necrosis in acute skin flaps and the surgical delay procedure reduces local production and also allows time to deplete the vasoconstricting and prothrombotic substances before converting the bipedicle flap to single-pedicle flaps. In the past, research in skin flap surgery was focused on the use of vasodilating and antithrombotic drugs to augment skin flap viability. So far, the outcomes of pharmacological therapy for the prevention or treatment of pedicle flap ischemic necrosis are disappointing and will be discussed later.

Surgical delay procedure induces vascular territory expansion by opening existing choke arteries

Pang *et al.* studied the capillary blood flow in delayed random-pattern pig skin flaps. We found that the capillary blood flow increased significantly within 2 days of delay and a maximum increase in skin flap capillary blood flow occurred between 2 and 3 days of delay, and remained unchanged between 4 and 14 days of delay without an increase in density of arteries (arteriogenesis) assessed by histology. This increase in capillary blood flow occurred mainly in the distal portion of the skin flap.¹⁰¹ Similar increase in capillary blood flow

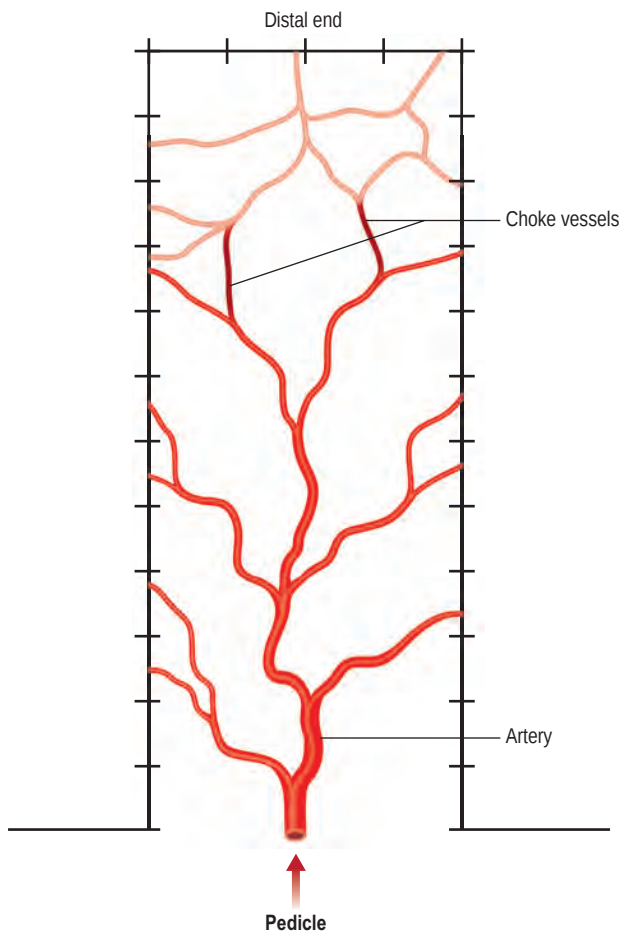


Fig. 23.5 Opening of existing blood vessels (choke vessels) in the distal portion of the surgically delayed skin flap.

was also seen in vascular delay of pig TRAM flaps within 3–4 days of delay and it is unlikely that an increase in arterial density (arteriogenesis) could have occurred during this short period of time. Therefore, these investigators described this phenomenon as vascular territory expansion by recruitment (opening) of existing arteries, as illustrated in Fig. 23.5.⁹⁰ Opening of existing blood vessels was demonstrated by Taylor and colleagues in vascular delay of skin flaps in the guinea pig, rabbit, dog, pig, and human,^{144–147} and by Yang and Morris in vascular delay of rat skin flaps,^{148,149} and this phenomenon was labeled by these investigators as angiosome territory expansion by opening of existing choke blood vessels.

Surgical delay procedure induces angiogenesis

Lineaweaver *et al.* reported that vascular delay increased the viability of the skin paddle of rat TRAM flaps and this protective effect of vascular delay was associated with a significant increase in gene expression of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF) in the skin paddle of the rat TRAM flaps within 12 hours of vascular delay. These investigators speculated that these cytokines induced vasodilation and angiogenesis to augment skin paddle viability in rat TRAM flaps.¹⁵⁰ The vascular

mechanism of surgical delay is still unclear. However, it was previously reported that the angiogenesis inhibitor endostatin inhibited ischemia-induced microvascular density and viability of mouse dorsal random-pattern skin flaps.¹⁵¹ Therefore, endostatin can be used in the future to investigate the role of angiogenesis and arteriogenesis in surgical delay in skin flap surgery in laboratory animals.

Pharmacological therapy for augmentation of pedicle flap viability

As discussed previously, the surgical delay procedure is costly and time-consuming. Therefore, much research has been focused on drug therapy for augmenting blood flow and viability in pedicle flap surgery.

Drug therapy against vasoconstriction and thrombosis in pedicle flap surgery

Vasoconstricting and prothrombotic substances such as NE, TXA₂, 5HT, and ET-1 are known to be elevated in skin flap surgery as a result of surgical trauma.^{121–131,135} These are very potent vasoconstrictors.^{134,136–142} In the past, research in skin flap surgery was focused on the use of vasodilating and antithrombotic drugs to augment skin flap viability. These studies were reviewed in detail up to 1990 by various investigators and will not be discussed here.^{3,117,152,153} The categories of drugs included: α -adrenoreceptor antagonists; drugs causing depletion of catecholamine in nerve terminals; drugs preventing catecholamine release from the nerve terminal; β -adrenoreceptor agonists; direct vasodilators, calcium channel blockers, hemorrhheological drugs; vasodilating eicosanoids and their synthesis inhibitors; anti-inflammatory drugs; drugs inhibiting adherence and accumulation of neutrophils; and free radical scavengers. More recently, research in drug therapy for augmenting flap viability also focused on vasodilation,^{154–170} antithrombosis,¹⁷¹ and inhibition of neutrophil from adherence and accumulation.¹⁷² In general, the results with these vasodilating and antithrombotic drug treatments in augmenting pedicle flap viability were controversial, inconclusive, or very modest at best, compared with surgical delay. Finally, most of these studies were performed in loose-skinned laboratory animals (e.g., rats, rabbits) whose skin vasculature and anatomy are likely different from those of the human.⁷⁸ Using more clinically relevant pig pedicle skin flap models, Pang and colleagues tested several drugs, which were reported to augment rat skin flap viability by other investigators. We found that neither skin blood flow nor viability was significantly improved by the following categories of drug: glucocorticoid,¹⁷³ α -adrenoreceptor antagonists,⁸⁸ vascular smooth-muscle relaxants,^{174,175} β -adrenoreceptor agonist,¹⁷⁴ TXA₂ synthesis inhibitor,¹⁷⁴ TXA₂ receptor antagonist,¹⁷⁴ and vasodilating prostanoids.¹⁷⁶ We also found that 5HT₂ receptor antagonists augmented skin flap viability in the pig, but the beneficial effect was modest compared with surgical delay.^{174,177} In conclusion, the mechanism of surgical or vascular delay is unclear. So far, there is no effective drug therapy which can mimic surgical or vascular delay in augmenting skin flap viability.

Angiogenic cytokine protein or gene therapy for augmentation of pedicle flap viability

Angiogenic cytokines such as VEGF, FGF, and platelet-derived growth factors (PDGF) are known to induce an increase in capillary density (angiogenesis). Recently, flap research has been focused on the use of local angiogenic cytokine protein therapy to augment flap viability. For example, improved viability was observed following local subdermal injection of VEGF₁₆₅ immediately after elevation of rat dorsal random-pattern skin flaps;^{178,179} local interarterial injection of VEGF₁₆₅ immediately after raising of rat epigastric island skin flaps;^{180,181} and injection of VEGF₁₆₅ into the rectus abdominis muscle 20 days before construction of TRAM flaps in the rat.¹⁸² There is also evidence to indicate that FGF can augment skin flap viability. This has been observed following intradermal injection of FGF 30 minutes before surgery in rat dorsal random-pattern skin flaps;¹⁸³ subdermal injection of FGF immediately after surgery and at 48 hours postoperatively in rat dorsal random-pattern skin flaps;¹⁸⁴ and subdermal injection of FGF 18 days before construction of arterial skin flaps in mouse ears.¹⁸⁵ Last but not least, it was reported that local PDGF treatment mimicked the surgical delay phenomenon in augmenting latissimus dorsi muscle viability in the mouse.¹⁸⁶ So far none of these angiogenic cytokines has been tested on tight-skinned animals such as the pig. Since the angiogenic cytokines were effective in augmenting skin flap viability when given several days before or immediately after surgery, it is possible that vasodilation may play an important role in this mechanism. Khan *et al.* in our laboratory used the rat dorsal random-pattern skin flap model to study the mechanism of acute local intradermal VEGF₁₆₅.¹⁸⁷ These studies showed that subdermal injection of VEGF₁₆₅ at the time of surgery effectively attenuated pedicle skin flap ischemic necrosis in a dose-dependent manner, mainly by inducing the synthesis/release of the vaso-relaxing factor NO. The mechanism by which VEGF₁₆₅ augmented skin flap viability appeared to depend on the vasodilator effect of VEGF₁₆₅ in the early stage (within 6 hours) after surgery, followed by the angiogenic effect (i.e., increase in capillary density) of VEGF₁₆₅ in the later stage after surgery. It is important to point out that VEGF₁₆₅ is a potent vasodilator in skin vasculature. Specifically, we observed that VEGF₁₆₅ was seven times more potent than acetylcholine in inducing skin vasodilation in isolated perfused pig island buttock skin flaps.¹⁸⁸

The biological half-life of VEGF₁₆₅ is 30–45 minutes in normoxic and 6–8 hours in hypoxic conditions.¹⁸⁹ It is possible that the effectiveness of VEGF₁₆₅ protein therapy is limited by its short half-life and VEGF₁₆₅ gene therapy may be the key to providing a steady release of VEGF₁₆₅ perioperatively.¹⁹⁰ Specifically, local intradermal or subcutaneous injection of liposomal or adenoviral vectors encoding the cDNA of VEGF₁₆₅ (Ad.VEGF₁₆₅) given at 0.5, 2, 3, 7, or 14 days before surgery was shown to augment skin flap viability in the rat.^{191–194} Local subcutaneous injection of VEGF₁₆₅ plasmid DNA 7 days preoperatively also increased skin viability in rat musculocutaneous (TRAM) flaps.¹⁹⁵ Of interest is the observation that the number of capillaries and arterioles were significantly increased in the skin of rat musculocutaneous (TRAM) flaps when Ad.VEGF₁₆₅ was injected subcutaneously 14 days before surgery.¹⁹⁶ However, it is important to point out that review of the data in the literature to date indicates that the efficacy

of rat dorsal skin flap viability augmentation was similar between VEGF₁₆₅ protein and gene therapy, and the skin flap viability was about 15–20% lower than that of surgical delay.^{187,197} Therefore, more than VEGF₁₆₅ is required to mimic surgical delay in augmenting flap viability.

Pharmacological therapy for augmentation of free flap viability

Vasospasm, thrombosis, and ischemia–reperfusion injury are the main causes of free flap failure. At the present time, there are relatively safe drugs which are used clinically to prevent or treat vasospasm and thrombosis in flap surgery. However, drug therapy for ischemia–reperfusion injury remains a subject of animal research.

Drug therapy for prevention of vasospasm and thrombosis in free flap surgery

Drug therapy is used by some surgeons to prevent or treat anastomotic vasospasm and thrombosis in free flap surgery. These drugs can be classified into three categories and their dosage, efficacy, and treatment guidelines have been reviewed.^{198–200}

Anticoagulant agents

Heparin, aspirin, and dextran are the three common anticoagulants used in microsurgery, but their efficacy is unclear. For example, it has been reported that intravenous heparin treatment reduced the incidence of anastomotic thrombosis when given before the restoration of blood flow in the rabbit.²⁰¹ Subsequently, results from two clinical studies in free flap surgery indicated that low dosage of intraoperative heparin treatment (3000 or 5000 units intravenously) did not increase the rate of hematoma formation or intraoperative bleeding. However, these low doses of heparin treatment also did not have any significant effect on the prevention of microvascular thrombosis.^{202,203} Obviously, a higher systemic dose of heparin is required. Some surgeons recommend an intraoperative bolus injection of 100–150 units/kg of intravenous heparin before cross-clamping and a supplement injection of 50 units/kg of heparin every 45–50 minutes until re-establishment of blood flow after anastomosis.²⁰⁴ However, this is not common practice. More clinical research is required to identify an effective dose of heparin for the prevention of anastomotic thrombosis without hematoma formation in free flap surgery.

It was observed in the rabbit that a low dose of aspirin (10 mg/kg) caused an antithrombotic effect because it reduced TXA₂ (vasoconstrictor) formation in the platelet to a greater extent than PGI₂ (vasodilator) formation in the endothelium.²⁰⁵ Low doses of aspirin were also observed to inhibit anastomotic thrombosis and improve the microcirculation in the rat.²⁰⁶ In humans, lower doses of aspirin (40–325 mg) were observed to inhibit platelet cyclo-oxygenation production of TXA₂ with minimal inhibition of endothelium-derived production of PGI₂.^{207–209} However, more than 24 hours are required to achieve maximal cyclo-oxygenation inhibition.^{207,210} It was also reported that a low oral dose of aspirin (325 mg/day) did not cause postoperative hematoma formation in

clinical free flaps.²¹¹ Furthermore, there is clinical evidence to indicate that a low dose of aspirin is effective in preventing coronary graft occlusion given preoperatively or within 24 hours of surgery.^{212,213}

The low-molecular-weight dextran 40 (MW 40000) and dextran 70 (MW 70000) are known to have blood volume expansion and antithrombogenic effects in humans.²¹³ Dextran 40 is the most popular dextran used to decrease platelet aggregation and to improve blood flow in free flap surgery. The effective doses have been reviewed elsewhere.²⁰⁰ However, dextran 40 also has undesirable side effects such as anaphylaxis, pulmonary and cerebral edema, and renal failure.²¹⁴ In addition, there is clinical evidence to indicate that pre- or postoperative low-molecular-weight dextran treatment may not be effective in augmenting free flap viability.^{215–217}

Thrombolytic agents

While early detection and re-exploration are crucial for salvaging failing free flaps, those flaps unresponsive to standard interventions may benefit from the selective use of thrombolytics for lysing formed thrombi.²¹⁸ The common thrombolytic agents that have been used successfully in clinical free flaps are streptokinase,^{219–227} and recombinant tissue plasminogen activator (tPA).^{228–231} The effective doses of these thrombolytic agents have also been discussed.^{199,200} Results from these studies are encouraging and these agents are now commonly used, particularly in take-back situations. However, most, if not all, of these studies were small or in the form of case reports.

Antispasmodic agents

Papaverine, nifedipine, and lidocaine are the most common topical antispasmodic drugs used in clinical microsurgery. Papaverine is an opiate alkaloid, which relaxes vascular smooth muscle, especially during spasms. It inhibits phosphodiesterase, the enzyme involving the breakdown of cyclic adenosine monophosphate (cAMP), resulting in accumulation of cAMP, causing vasodilation.²³² Nifedipine is a calcium channel blocker. The mechanism of action is inhibition of calcium influx into the arterial smooth-muscle cells, thus causing smooth-muscle cell relaxation.²³³ The vasodilator effect of lidocaine is the result of its effect on the Na⁺/Ca²⁺ ion exchanger pump causing a reduction in intracellular calcium content, resulting in vasodilation.²³⁴

Preischemic and postischemic pharmacological conditioning against ischemia–reperfusion injury in free flap surgery

In the past 20 years, research in ischemia–reperfusion injury in cardiac and skeletal muscle has been focused on the efficacy and mechanism of preischemic and postischemic conditioning against ischemia–reperfusion injury.²³⁵ This information is important because it may provide insight into the identification of new drugs for the prevention or salvage of skin and skeletal muscle from ischemia–reperfusion injury in free flap and replantation surgery.

Local preischemic conditioning against ischemia–reperfusion injury in skeletal muscle

The phenomenon of preischemic conditioning against ischemia–reperfusion injury was first recognized in dog myocardium.²³⁶ Subsequently, Mounsey *et al.* in our laboratory demonstrated this phenomenon for the first time in pig muscle flaps.^{237,238} Specifically, we reported that instigation of three cycles of 10 minutes occlusion/reperfusion in pig latissimus dorsi muscle flaps with a vascular clamp reduced the muscle infarction by 40–50% when these muscle flaps were subsequently subjected to 4 hours of warm ischemia and 48 hours of reperfusion. This observation was confirmed with pig gracilis muscle flaps in our laboratory.^{239,240} Subsequently, other investigators reported that local preischemic conditioning also augmented ischemia–reperfusion injury tolerance in rat skeletal muscle,^{241–243} and in the skin of cutaneous and musculocutaneous flaps in the rat.^{244,245} Local preischemic preconditioning also attenuated vascular dysfunction in rat skeletal muscle²⁴⁶ and capillary no-reflow in rat and dog skeletal muscle induced by sustained ischemia and reperfusion.^{247,248} However, local preischemic conditioning has clinical limitations because it requires instigation of brief cycles of ischemia and reperfusion by repeated clamping of the vascular pedicle and there is the risk of damaging the blood vessels. However, understanding the mechanism of local preischemic conditioning may provide insight into the identification of pharmacological treatment to mimic local preischemic conditioning. Using pharmacological probes, we uncovered that the mechanism of local preischemic conditioning in pig latissimus dorsi muscle flaps involved adenosine A₁ receptor–protein kinase C–mitochondrial K_{ATP} channel-linked events.^{249–254} Martou *et al.* in our laboratory demonstrated the efficacy of preischemic conditioning against ischemia–reperfusion injury in *ex vivo* human rectus abdominis muscle strips.⁶² This model is now being used to study the pharmacological preischemic conditioning against ischemia–reperfusion injury in *ex vivo* human skeletal muscle strips.

Remote preischemic conditioning against ischemia–reperfusion injury in skeletal muscle

Of interest was the report from Oxman *et al.* that the instigation of a 10-minute cycle of occlusion and reperfusion in a hind limb by tourniquet application preconditioned the heart against reperfusion tachyarrhythmia in the rat.²⁵⁵ This is known as remote preischemic conditioning. Based on this technique, Addison *et al.* in our laboratory demonstrated for the first time the efficacy of noninvasive hind limb remote preischemic conditioning for the global protection of skeletal muscle against ischemia–reperfusion injury.²⁵⁶ Specifically, we demonstrated that the instigation of three cycles of 10 minutes of occlusion/reperfusion in a hind limb of the pig by tourniquet application (~300 mmHg) under general anesthesia protected multiple skeletal muscles at various distant locations from infarction when these muscles were subsequently subjected to 4 hours of ischemia and 48 hours of reperfusion (Fig. 23.6). We also observed that mitochondrial K_{ATP} channels play a central role in the trigger and mediator mechanisms of hind limb remote preischemic conditioning of pig skeletal muscle against infarction.²⁵⁷

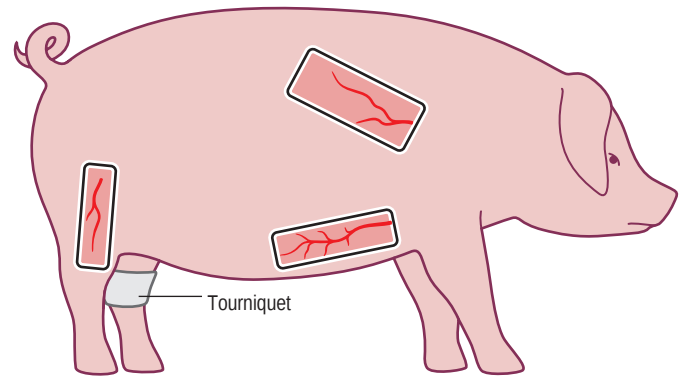


Fig. 23.6 Noninvasive remote preischemic conditioning for global protection of skeletal muscle against ischemia–reperfusion injury. Instigation of three cycles of 10 minutes occlusion/reperfusion in a hind limb of the pig by tourniquet application (~300 mmHg) protected latissimus dorsi, gracilis, and rectus abdominis muscle flaps from infarction when subsequently subjected to 4 hours of ischemia and 48 hours of reperfusion.

Subsequently, Moses, another of our research fellows, demonstrated that the infarct-protective effect of remote preischemic conditioning in pig skeletal muscle was biphasic²⁵⁸ and the time course was similar to that seen in local preischemic conditioning in the myocardium of rabbits^{259–261} and dogs²⁶² and in the skeletal muscle of rats.^{263,264} Specifically, an early phase of infarct protection started immediately after hind limb remote preischemic conditioning, waned within 4 hours, and completely disappeared in less than 6 hours after remote preischemic conditioning (Fig. 23.7). The late phase (second window) of infarct protection (re) appeared within 24 hours after hind limb remote preischemic conditioning and lasted up to 72 hours. More importantly, it was observed that sarcolemmal and mitochondrial K_{ATP} channels play a central role in the trigger and mediator mechanism, respectively.²⁵⁸ The logical approach in the future is to identify a nonhypotensive prophylactic drug (e.g., sarcolemmal K_{ATP} channel opener) to be taken orally 24

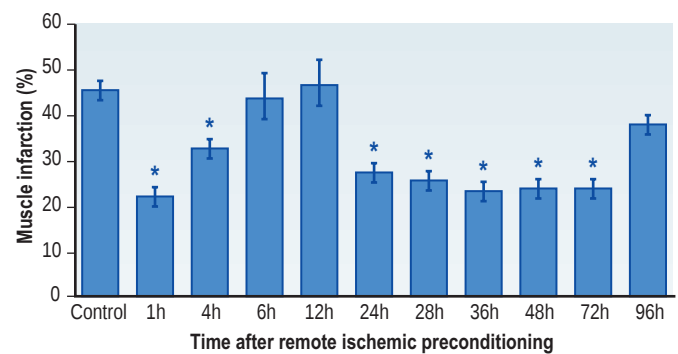


Fig. 23.7 Biphasic time course of the infarct-protective effect of remote ischemic preconditioning. Muscle flaps in control and treatment groups were subjected to 4 hours of ischemia and 48 hours of reperfusion. In the treatment groups, 4 hours of ischemia began at 0, 4, 6, 8, 24, 28, 36, 48, 72, or 96 hours after remote ischemic conditioning. Infarct protection occurred at 0–4 hours and 24–72 hours after remote ischemic conditioning. Values are mean ± SEM; n = 8 flaps. Means with an asterisk are similar and are significantly different from the means without an asterisk (n = 8 flaps, P < 0.05).

hours before surgery to achieve 48 hours of uninterrupted perioperative protection of skeletal muscle from ischemia–reperfusion injury in elective microsurgery. Recently, we observed in pigs that the clinical drug nicorandil induced 48h uninterrupted muscle infarct protection 24h after intravenous injection.²⁶⁵

Postischemic conditioning for augmentation of free flap viability

Khiabani and Kerrigan reported that local intra-arterial infusion of the NO donor SIN-1 to pig latissimus dorsi myocutaneous flaps and buttock cutaneous flaps by means of a catheter for 18 hours after 6 hours of ischemia was effective in salvaging the ischemic skin and muscle from reperfusion injury.²⁶⁶ However, this technique is too invasive for routine clinical use. McAllister *et al.* in our laboratory reported that instigation of four cycles of 30-second reperfusion/reocclusion at the onset of reperfusion after 4 hours of ischemia reduced pig latissimus dorsi muscle flap infarction by ~50%, assessed at 48 hours of reperfusion.²⁶⁷ This phenomenon is known as postischemic conditioning and was first demonstrated in dog myocardium.²⁶⁸ Subsequently, Park *et al.* demonstrated that postischemic conditioning also protected contractile function of rat extensor digitorum longus muscle subjected to 3 hours of ischemia and 5 days of reperfusion.²⁶⁹ McAllister also demonstrated that the mechanism of postischemic conditioning in pig skeletal muscle involved lowering of mitochondrial free Ca^{2+} content, closing of mitochondrial permeability transitional pores (mPTP), and increase in muscle ATP content. The infarct-protective effect of postischemic conditioning was mimicked by intravenous injection of the mPTP opening inhibitor cyclosporine A (10 mg/kg) at 5 minutes before reperfusion.²⁶⁷ This observation suggests that cyclosporine A may be a potential clinical therapeutic agent for salvaging ischemic replants and muscle free flaps from reperfusion injury. Mowlavi *et al.* reported that preischemic or postischemic cyclosporine A treatment (15 mg/kg, orally) increased rat gracilis muscle viability when subjected to 4 hours of ischemia and 24 hours of reperfusion.²⁷⁰ However, statistical significance was achieved in preischemic treatment but not postischemic treatment. A higher oral dose of cyclosporine A may be required for postischemic treatment because, according to McAllister *et al.*, the effective dose of cyclosporine A for postischemic conditioning in pig skeletal muscle flap was 10 mg/kg intravenously.²⁶⁷ At the present time, an *in vitro* model is being used in our laboratory to study the efficacy and mechanism of cyclosporine A in salvage of *ex vivo* ischemic human rectus abdominis muscle from reperfusion injury.^{271,272}

Recently, McAllister *et al.* also reported that preischemic or postischemic treatment with the Na^+/H^+ exchanger inhibitor cariporide (3 mg/kg, intravenously) induced a significant decrease in mitochondrial free Ca^{2+} content and infarct size in pig latissimus dorsi muscle flaps when subsequently subjected to 4 hours of ischemia and 48 hours of reperfusion.²⁷³ This observation further supports our finding that the mechanism of postischemic conditioning involves lowering of mitochondrial free Ca^{2+} content and inhibition of opening of the mPTP, and the mPTP opening inhibitor cyclosporine A is effective in salvage of ischemic pig skeletal muscle from reperfusion injury.

Conclusion and future directions

Flap pathophysiology

Surgical and vascular delay are the only proven clinical techniques for augmentation of pedicle skin flap viability. However, these surgical manipulations are time-consuming and costly. Similarly, preischemic and postischemic conditioning are effective in protecting skeletal muscle flaps from ischemia–reperfusion injury in laboratory animals, but surgeons are reticent to conduct a clinical trial on the efficacy of ischemic preconditioning and postconditioning against ischemia–reperfusion injury in free flap surgery because these techniques are invasive and/or time consuming. Therefore, there is the need to continue to search for pharmacological therapy to increase skin blood flows and distal perfusion in pedicle skin flaps and to protect the skin and muscle from ischemia–reperfusion injury in free flaps and replant surgery.

Flap pharmacology

The angiogenic cytokine VEGF₁₆₅ is known to cause local vasodilation and increases in capillary density (angiogenesis), resulting in augmentation of skin blood flow and viability in random pattern skin flaps in the rat. However, review of the literature thus far indicates that the skin flap viability in VEGF₁₆₅ gene or protein therapy was about 15–20% lower than that of surgical delay.^{187,197} In addition, angiopoietin-2 is known to induce arteriogenesis in mouse ischemic hind limb.²⁷⁴ Therefore, future studies are recommended to investigate if combined local VEGF₁₆₅ and angiopoietin-2 protein or gene therapy will synergistically increase capillary and arteriole density, resulting in maximizing skin viability in random skin flaps.

In the cases of ischemic–reperfusion injury in skeletal muscle, future studies are required to understand the mechanism of preischemic and postischemic conditioning in protecting skeletal muscle against ischemic–reperfusion injury in laboratory animals *in vivo* and human skeletal muscle *in vitro*. This probably will include studying the role of Na^+/H^+ exchangers, mitochondrial free Ca^{2+} content, and opening of the mPTP in the pathogenesis of ischemia–reperfusion injury. This area of research will most likely lead to the identification of pharmacological agents to protect skeletal muscle from ischemia–reperfusion injury when given before or after ischemia. Further studies are also recommended to investigate the additive effect of combined preischemic and postischemic pharmacological conditioning to protect skeletal muscle from ischemia–reperfusion injury. Last but not least, our published human skeletal muscle strip culture technique⁶² is recommended for screening drugs for clinical studies of preischemic and/or postischemic pharmacological conditioning of skeletal muscle against ischemia–reperfusion injury.^{62,272,275}

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Principles and techniques of microvascular surgery

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SYNOPSIS

- Microvascular surgery refers to the surgical coaptation of small vessels usually around 1 mm in diameter under microscope magnification. Microsurgery is a broader term not only limited to blood vessels but also refers to coaptation of tiny nerves and lymphatics.
- This technique has evolved significantly over the last four decades, starting from revascularization and replantation in 1960 to free-flap surgery.
- The development of the operating microscope, microinstruments, and ultra fine sutures have greatly aided its widespread use.
- Despite various techniques having been developed for the handling of small vessels, the most commonly used techniques are still the end-to-end and end-to-side anastomosis and coupling devices. Difficult situations such as vessel diameter discrepancy, inadequate vessel length, and poor vessel quality can usually be overcome with special techniques.
- Advances in microsurgery leading to consistently high success rates have made free tissue transfer a cost-effective, first-line option in modern reconstructive surgery with superior results and high patient satisfaction compared with conventional methods. Microsurgery, however, is mentally and physically demanding. The need for special training cannot be overemphasized.
- Thorough preoperative planning, flexibility of the surgical plan, and flawless execution are mandatory for successful free flap surgery.
- Clinical assessment remains the gold standard in free flap monitoring. Early detection of a failing free flap with prompt intervention greatly improves the salvage rates. Pharmacological agents such as low-dose heparin, PGE1 and dextran are also useful. Complications of free tissue transfer are not only due to vascular compromise; inadequate planning, inappropriate flap selection and/or flawed execution can compromise the flap and/or the functional and aesthetic outcomes.
- Refined microsurgical techniques and improved postoperative care such as specialized microsurgical intensive care units have led to a 96–98% success rate in developed centers nowadays. If the first microsurgical reconstruction fails, a second microsurgical reconstruction can still be attempted with good results after identifying and managing potential causes.

- Microsurgery will not decline but will continue to evolve. Microsurgery has indeed revolutionized our approach to reconstructive challenges, and with further refinements, we will see an even wider application; particularly, in the fields of supermicrosurgery, free-style free flaps, and composite tissue allotransplantation.

Introduction

Microsurgery is a general term for surgery requiring the operating microscope. Depending on the structure operated on and its size, terms such as microvascular surgery (surgery on blood vessels around 1 mm), microneural surgery, micro-lymphatic surgery, and microtubular surgery, etc., can be coined.

Supramicrosurgery is an extreme microsurgery and refers to anastomoses of vessels around 0.5 mm in diameter (0.3–0.8 mm), invaluable in lymphatic reconstruction and perforator-to-perforator anastomosis.^{1,2}

Reconstructive microsurgery utilizes microsurgical and supramicrosurgical techniques in procedures such as revascularization, replantation, and auto- or allotransplantation to solve problems arising from traumatic injuries, congenital deformities, and tumor ablation. However, some of these procedures are performed under loupe magnification ($\times 2.5$ – 8), including vessel coaptation, especially when the diameter is not too small (usually around 3 mm).

It is worth noting that microsurgical techniques and, to a lesser degree, supramicrosurgery are not limited to plastic surgery; however, the scope of practice within plastic surgery remains the most diverse in modern surgery.

The era of microsurgery began with the invention of the microscope in 1920. But the improvement in magnification and illumination and the development of microinstruments and ultrafine sutures are the leading factors for the widespread use of the techniques.

Our approach to micro- and supramicrosurgery has changed over time. Consistently reported high success

rates of 97–100%, cost-effectiveness, superior functional, aesthetic, and psychological outcomes compared with other techniques have changed the indication for microsurgery from being the last resort after failure of other options into the first choice and reversed, as a result, the reconstructive ladder.

However, and not being confused as a “double-edged sword”, microsurgery comes with a high price, demanding experience and resources. But with professional training, specialized infrastructures, dedication, and support, microsurgery can be performed daily with convenience.

The focus of this chapter is the principles and techniques of basic and advanced microsurgery and free tissue transfer, including perforator free flaps, free-style free flaps, allotransplantation, and possible future directions. Revascularization and replantation are specifically covered in other chapters.



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Tools

Since the introduction of the triangulation technique for vessel repair by Alexis Carrel, the diameter of vessels that can be anastomosed has become progressively smaller, due largely to developments in surgical techniques, surgical instrumentation and microsutures, and improved optics in present-day microscopes.

Magnification under adequate illumination allows more accurate perception of operative anatomy and positioning of instrumentation, with improved outcomes and facilitation of procedures that would be impossible to undertake without assisted vision. Intraoperative magnification also reduces surgeons' fatigue as a result of improved ergonomics. Two types of optical system are used by surgeons to produce magnification – the surgical microscope and loupes.

Surgical microscopes

The basic sophistication of today's operating microscope includes binocular head with adjustable eyepieces and a teaching head to allow two people to work with magnification in the operating field; there could be a third head for digital recording. The heads should independently pivot and have separate magnification levels with the flexibility to be retrofitted with a camera to document the procedure on an SD card or DVD as well as to allow colleagues to view the operation in real time.

Tilt, focus, and zoom can be controlled via a foot pedal or a hand control panel; the first keeps the surgeon's hands free to perform the surgery without interruption, but necessitates coordination; the second option could be more practical as it keeps all functions in one accessible place.

Antimicrobial-coated surfaces and internally routed cables are very important because the controls, lighting, and documentation technology nowadays require wiring; loose wiring can get in the way of the surgical team and can harbor bacteria.

40× magnifications can be provided by some microscopes with instant magnification change, a variable working distance, and precise XY positioning.

Some microscopes such as Leica and OPMI Pentero incorporate intraoperative fluorescence tools to assist the surgeon, which is an invaluable technique to check perfusion before and after, in lymphatic microsurgical reconstruction, and precise tumor ablation in neurosurgery.

The modern operating microscope can be mounted on a stand, placed on a table top, or worn on the surgeon's head. Some of them can be hung on the ceiling or wall to conserve floor space in the surgical suite. Microscopes that can be moved from one room into another and used by different surgical specialties are very desired and cost-effective; however, ophthalmic surgical microscopes could be an exception due to the specialized lighting, focusing, and magnification requirements.

When using the microscope, choosing the appropriate level of magnification is important in order to maneuver the instruments and perform the anastomosis efficiently. Low magnification (6×–12×) can be used for vessel preparation and suture tying while middle magnification (19×–15×) can be used for suture placement. High magnification is usually only required for very small vessel anastomosis and inspection of the anastomosis. For tips for use, see [Box 24.1](#).

Loupes

Loupes can provide magnifications of 2.5×–8× and may be mounted on glasses or headbands. They are cost-effective, portable, and offer operator freedom.³⁰ Enhanced visualization provided by loupes is invaluable for precise dissection of tissues and placement of instruments and sutures. In experienced hands, high-magnification loupes can even provide an effective alternative to the operating microscope for vessels as small as 1 mm. A retrospective study of 200 consecutive free microvascular tissue transplantations compared the performance of free tissue transplants with 3.5× loupes and the operating microscope.²⁴ There was no difference in outcome between the two groups, with free-flap success rates of 99% for both the loupe and the microscope groups. However, microscopes were required when performing anastomoses in children and on vessels of 1.5 mm or less in diameter. Despite these studies, most centers still use the microscope for its greater range of magnification and light sources. This is particularly important for smaller-vessel anastomoses in the era of perforator flap, free-style, and supramicrosurgery practice.

BOX 24.1 Tips for using surgical microscopes

- Familiarize yourself with the microscope
- Spend time getting the position right, making sure that the interpupillary distance and diopter correction are right
- Use an adjustable seat if you intend to sit
- Sit comfortably with feet flat on the ground to provide a stable base
- Upper extremities should be well supported, resting on folded drapes as necessary, to minimize fatigue and tremor
- Focus should be adjusted with the scope at highest magnification before starting

Historical perspective

The concept of vascular repair was first proposed by Paré in 1552. However, it was two centuries later before the first successful brachial artery repair was performed in 1759³ and even later in 1897 when Murphy reported his successful end-to-end anastomosis of the femoral artery by invagination of vessels with fine silk.⁴ Building on Murphy's work, Alexis Carrel reported a technical breakthrough for performing end-to-end vascular anastomoses using the triangulation method in 1902.⁵ This work was further expanded in collaboration with Guthrie, and for his contributions in "vascular suture and the transplantation of blood vessels and organs", Alexis Carrel was awarded the Nobel Prize in 1912.

Experimental limb replantation in dogs and other models continued in microvascular surgery. However, it was the isolation of heparin from the liver by a medical student, McLean,⁶ and its clinical introduction as an anticoagulant to control clotting two decades later⁷ as well as the use of the operating microscope that gave microvascular surgery a giant leap forward.

The compound microscope was invented by Janssen in 1590 and subsequently mass-produced by Carl Zeiss for laboratory research in the late 1800s. However, it was not until 1921 that Carl-Olof Siggesson Nylen, a Swedish otologist, first used a modified monocular Brinell-Leitz microscope for animal surgery and then, later in November of the same year, in a patient with chronic otitis and pseudofistula symptoms.⁸ Nylen's microscope was soon replaced by a binocular microscope, developed in 1922 by his colleague Gunnar Holmgren. In 1946, Perritt applied the use of the microscope to ophthalmology.

The stage for modern microvascular surgery was set in 1960 when vascular surgeons Jacobson and Suarez^{9,10} introduced the diploscope, a stereoscopic microscope for simultaneous use by two surgeons, for anastomoses of vessels as small as 1 mm in diameter. From this point onwards, the microscope found extensive use in the fields of peripheral nerve surgery,^{11,12} plastic and reconstructive surgery,¹³ experimental transplantation,¹⁴ and neurosurgery.

The first clinical application of microvascular surgery was in replantation. Malt and McKhann first reported the successful replantation of several arms in 1964¹⁵ whilst the first complete thumb replantation was performed in 1965 by Konatsu and Tamai with the aid of a microscope.³ Young

reported on their series of second toe-to-hand transfers in 1966¹⁶ and a year later, Cobbett performed the first successful great toe-to-thumb transfer in a human being.¹⁷

The first experimental flaps based on the superficial epigastric vessels were transplanted in dogs and reported by Krizek *et al.* in 1965.¹⁸ Antia performed the first clinical free flap, but this was only reported several years later, in 1971.¹⁹ This dermolipomatous groin flap for facial defect reconstruction was, however, complicated by infection and at least partial necrosis occurred. In 1970, the omental free flap by McLean and Buncke was the first fully successful free flap²⁰ and in 1973, Daniel and Taylor reported transfer of the first groin flap.²¹

New flaps, mainly musculocutaneous, were designed next and the indications for their use were expanded over the next few decades. Complication and failure rates declined^{22,23} and success rates today range between 95.9 and 99%,^{24,25} compared to 74–91%²² in earlier times.

During the late 1980s and into the 1990s, research focused on anatomy, flap physiology, better donor sites, and improved survival. But it was not until the late 1980s that cutaneous flaps based on perforator vessels finally evolved from conventional musculocutaneous flaps, and intramuscular dissection was born with preservation of function and major vessels. The first true perforator flap was the deep inferior epigastric artery perforator flap first reported in 1989 by Koshima and Soeda.²⁶ The next milestone in free flap surgery was the free-style flap that allowed the harvest of a paddle of skin based on an audible perforator detected by a hand-held Doppler in an area that had not been previously adequately studied, alleviating concerns regarding vascular anomaly and leaving the door open for up to 400 perforator flaps.

Reconstructive microsurgery witnessed another great achievement when allotransplantation became a reality after the first successful hand transplantation in 1998 in Lyon, France, and in January of 1999 in Louisville, USA.^{27,28} The international experience has reached 107 transplanted hand/upper extremities in 72 patients by the year 2014.²⁸

The first partial face transplantation was performed in 2005 in Lyon, France, too. However, the first total face transplantation was performed in 2010 in Barcelona, Spain. So far, 29 partial, near-total, and total face transplantations have been performed.²⁹

It is worth saying, though, that the widespread application of allotransplantation will not depend on advances in microsurgery as much as immunosuppression!

Types

Two types of loupe are used in surgery: the compound (Galilean) and prismatic loupe. In contrast to single-lens off-the-shelf magnifying reading glasses, compound loupes have significantly superior optics. These consist of two magnifying lenses separated by air, achieving higher magnification, greater depth of field, and better working distance. However, image quality tends to become distorted at magnifications above 2.5 $\times$ and all such lenses create a “halo” effect at the periphery of the visual field which may disturb the surgeon. These drawbacks are counterbalanced by their relatively low cost and light weight and they are widely used and available from most manufacturers.³¹

Prismatic loupes provide higher optical quality because of a Schmidt prism, which lengthens the path of light through a series of mirror reflections inside the loupe. They can provide improved magnification, wider fields of view, and longer depths of field or working distance, but are 30–40% heavier, more expensive than compound loupes, and more easily damaged.³¹

Choosing loupes

While choice of magnification is largely dependent on the surgeon's preference, as a rough guide, a 2.5 $\times$ magnification is often sufficient for hand surgery and flap harvesting. If the loupes are to be used for perforator dissection or anastomoses, 3.5–4.5 $\times$ magnifications may be more suitable although 2.5 $\times$ is sufficient enough for perforator dissection. It is important to note that both the field of view and depth of field decrease with increasing magnification, while the weight of the loupes increases. Loupes with a magnification higher than 4.5 $\times$ tend to be cumbersome and too heavy for daily use (especially if they are prismatic), resulting in neck tension and increased fatigue. In such instances, opting for the microscope might be a better option.

Once the magnification has been chosen, other features such as lens design, working angle, and distances need to be considered. Some might choose to have the loupes mounted on glasses or headbands, while others might prefer through-the-lens (loupes mounted to the lenses of the frames) over the flip-up or snap-fit type. The latter permits cheaper changing of the magnification and the ability to change the lens prescription more conveniently. Some manufacturers can also supply headlights for use where additional lighting may be required – particularly useful with the use of higher magnifications.

Microsurgical instruments

Even with excellent optical systems, it would not have been possible for microsurgical techniques to have evolved without parallel refinements in microsurgical instruments and suture materials. Many fine instruments have been available for many years from jewelers but most have been developed during research on vascular, lymphatic, and neural microsurgery. A confusing array of instruments and supplies for microsurgery is now available, but with experience, most microsurgery can be done with surprisingly few instruments and most surgeons will become proficient with a reasonably small set.

Essential features in all microsurgical instruments include fine tips to spread, hold, or cut delicate tissue and suture, a nonreflective surface and comfortable handles that close easily to prevent fatigue.³² Many of the instruments used in microvascular surgery will also be spring-loaded, and choosing the right spring tension is important – too weak and the tips will close all the way just by holding the instrument; too firm and your hand will fatigue after a short period of use.

Most microinstruments are made of heat-hardened stainless steel, which is more resistant to wear and tear. They are prone to magnetization and should be stored on demagnetized or nonmagnetic shelves. If an instrument becomes magnetized, placing it in a coil demagnetizer attached to a regular alternating current supply and withdrawing it slowly will help. Antimagnetic materials such as titanium are becoming popular, promising to be rust-free and lighter in weight. In reality, however, they too can become magnetized. Most microinstruments are available with a round or flat handle, and range from 10–18 cm in length depending on surgeon preference and depth of working field. In general, shorter instruments are used when the anastomosis is closer to the surface, for example, in hand surgery, while instruments longer than 18 cm are used for procedures involving free tissue transfer. Longer instruments may also be balanced such that the balance point rests in the webspace. The slight counterweight at the end of the instrument reduces fatigue and allows better control and precision.

All instrument manufacturers give instructions for maintenance, and it is extremely important to follow these instructions to ensure maximal performance of the microinstruments. It is advisable to store the microinstruments in specially designed instrument cases and to protect their fine tips with silicone or rubber tubes. To be effective, they need to be fine-tipped with the jaws meeting precisely. The user should therefore minimize damaging them by not using them for anything other than handling vessels and nerves. Blood and contaminants should be regularly cleaned off by the scrub nurse during the course of surgery and finally rinsed with distilled or deionized water to avoid staining of the instruments. High chloride concentrations should be avoided as they lead to pitting and corrosion.

Types

Scissors

Microvascular scissors should be spring-loaded with sharp but gently curved blades and slightly rounded tips. When held closed, they can be used safely as a dissecting probe without the danger of damaging the vessel. Those designed for trimming the adventitia off the vessel end have straight blades with sharp tips and are also good for stitch-cutting.

Needle holders

Spring-loaded microvascular needle holders are held like pencils, resting on the first web. The handle is ideally rounded to allow the instrument to be rolled between the index and middle fingers and the thumb during the passing of the needle. Flat handles are also available. The jaws should be thin and gently curved with narrow shoulders to be able to grasp the microsutures. Needle holders could be also straight but the curved are usually finer at the tip and more suitable for vessel dilation. Some needle holders come with a ratchet

lock to facilitate the parking and passing of the needle; however, in inexperienced hands, the locking and unlocking maneuvers easily damage the needle and can cause significant trauma to the tissues handled; an unlocking needle holder is preferred.

Forceps

The jeweler's forceps were originally designed by the Swiss Dumont factory and is characterized by a flat handle and sharply narrowing tips. These tips must be aligned with a precision of 1/1000 inch, the diameter of the 10-0 nylon. When closed with moderate pressure, the jaws should meet evenly over a length of 3 mm so that the suture can be easily handled. They are further classified by the width of the contact surface, the narrowness, and the overall configuration. No. 2 forceps has wide jaws and can be used as needle holders. No. 3 forceps is straight and fine-pointed and no. 5 forceps has very fine tips. These are suitable for tissue handling and thus are commonly used in microsurgery. They are used almost continually in the nondominant hand for tissue handling, receiving the needle, and suture tying. No. 7 forceps has curved jaws. Microforceps are also available with round handles, although the flat handle is the preferred style. The most commonly used forceps are smooth-tipped, but the forceps can also be toothed, curved, angled, or equipped with a hole in the tip for better grasping. The angled forceps allows a grip that is parallel or perpendicular to the working surface and is useful for reaching under vessels, tying knots, and performing patency tests. A modified jeweler's forceps with a slender, smoothly polished nontapering tip can be used to dilate vessels gently.

Vascular clamps

The vascular clamps that are commonly used today have evolved significantly since the bulldog clamps that Jacobson used in his historical first microanastomoses, and many of the earlier models are now obsolete. The clamps developed by Henderson *et al.*³³ in 1970 required a small key and screw mechanism for adjustments and were not suitable for vessels less than 1.5 mm. In 1974, Acland³⁴ developed a double microvascular clamp with a small wire frame and a stay suture-holding device. Although it is still available today, it has largely been superseded by modifications of the design by Tamai³⁵ with the two clamps incorporated into a sliding bar.

Clamps are ideally atraumatic and have sufficient closing pressure to prevent bleeding and slippage but not damage the vessel wall. They are available as single clamps or double approximator clamps. In general, clamps are divided into those used on veins or arteries. Those designed for veins have a smaller closing pressure and usually a flat jaw all the way to the end. Those designed for arteries have greater closing pressure with a slight incurve at their tip to prevent crushing of the vessel wall. Generally, clamps marked with a V may be used for veins and most arteries, although particularly thick-walled veins may require the use of clamps marked with A.

To optimize closing pressure, clamps are available in a variety of sizes for different vessel diameters (i.e., the external diameter of the vessel in the natural state of full dilation). Pressure is inversely proportional to the vessel size – the

smaller the vessel inside the clamp, the higher the pressure exerted on the vessel by the clamp. Ideally, a clamp exerts a pressure of 5–10 g/mm² and 15–20 g/mm² when used on the largest and smallest vessels in its size range, respectively. Where possible, use the smallest appropriate clamp to minimize crushing the vessel with too large a clamp. Although they can be applied by hand or artery forceps, special clamp applicators for the smaller clamps are available to ensure the accurate placement and removal of the clamps without damage to the vessels and to the calibration.

In spite of the refinements, clamps, arguably, can cause intimal lesions, occupy space in confined sites and have a risk of backwalling due to vessel flattening. Plaque-filled atherosclerotic vessels could be a challenge. For all of these reasons, clampless anastomosis may be appealing to some surgeons. Preliminary clinical experience with a CE-certified thermosensitive gel clinically proven in cardiovascular surgery has been reported with high success rates.³⁶ The gel provides circular stenting and gentle distension of the vessels for a safe and blood-free anastomotic site, and it dissolves completely with cold saline irrigation after the anastomosis is done. This technique may find its way in atherosclerotic arteries and confined anastomosis sites, but more studies are warranted.

Bipolar coagulator

The development of the bipolar coagulator in 1956 promoted further development of microsurgery because a completely bloodless field was now attainable. The bipolar coagulator conducts current between the tips of the jeweler's forceps, producing heat damage only within a very small area between the instrument tips, allowing precise coagulation of small branches as close as 2 mm to the main vessel in place of vascular clamps.^{37,38} Its power setting must be optimized as too much power results in spreading of the heat with inadvertent damage to the surrounding tissues. Some surgeons prefer to use this for dissection instead of a knife or scissors, and bipolar scissors are now commercially available.

Irrigation and suction

Having a clear view of the vessel walls is imperative for successful anastomosis and even a small amount of blood may obscure the field. Constant irrigation with Ringer's lactate or heparinized saline and the use of suction are useful.^{39–41} Irrigation serves several purposes: to prevent desiccation of vessels, sticking of suture to tissue, to wash away blood and clots to provide a good view, and to wash away any prothrombotic factors that might act as a nidus for thrombus formation and to improve patency.^{42–44} This may be performed through a continuous irrigation system⁴⁵ with a smooth and blunt irrigation tip or more simply with a 5–10-mL syringe and a lacrimal cannula or 24-gauge angiocath.

There have been many suggested ways of suction, varying from suction through small segments of moistened hydrocellulose sponge or gauze, to suction tubes that drain through a perforated background plate and to homemade suction tips with an intravascular catheter attached to a 10-mL syringe placed over the normal suction tubing.⁴⁶ On occasion, when there is only a small amount of ooze, cellulose spearheads (eye sponges) on a polypropylene handle afford precise control and immediate absorption.

Microsutures

Buncke⁴⁷ described making his first microneedle by drilling a hole in a 75-mm stainless steel wire. This needle held a single strand of silk and was used to replant a rabbit's ear by anastomosis of 1-mm vessels. Soon a commercially available needle was developed by Acland,⁴⁸ working with the Springler-Tritt company.

Since then, microsurgical sutures have been available in combinations of different materials, suture sizes (8-0 to 12-0), tensile strengths, and needle configurations. The microsuture is considered to be the standard means of vascular anastomosis. The most widely used sutures are 9-0 monofilament nylon on a 100- μ m curved needle and 10-0 nylon on a 75- μ m needle. The choice is usually made based on the vessel wall thickness and diameter, with 9-0 sutures used for vessels of 2 mm or more in diameter and 10-0 for those between 1 and 2 mm in diameter. Smaller suture-needle combinations are available but reserved for use by experienced microsurgeons with very fine instruments, for very distal fingertip replantations, anastomoses in small children, and in lymph vessel anastomosis. Microneedles are typically shaped as three-eighths of a circle but are also available as a half-circle or straight (rarely used now), with round, tapered, or spatula-shaped tips to prevent damage to the fragile vessel wall. The commonest suture used in microsurgery is nonresorbable nylon which has low tissue reactivity and knot-holding ability, although polypropylene is preferred by some as it slides and handles better within the tissue.

Special considerations for supermicrosurgery

Supermicrosurgery was coined by Isao Koshima to describe anastomosis of blood vessels smaller than 1 mm (0.3 to 0.8 mm).¹ The technique has its application, mainly in very distal replantation, lymphatico-venous anastomosis, and perforator flaps.^{1,2} Special instruments are crucial for success. These instruments include a surgical microscope with the highest currently available magnifying power, with 50 $\times$ magnification, the thinnest titanium forceps, and the smallest surgical needle (12-0 nylon).

The microscope has high-power (50 $\times$) magnification and allows a 20-cm working distance, which was impossible with microscopes of 20 $\times$ magnification.²

Anastomotic devices

Despite the fact that microsutures are nowadays relatively inexpensive, reliable, and readily available, they do not fully meet the criteria of an "ideal" anastomosis. Many nonsuture techniques have developed in the search for faster and less traumatic anastomosis.

In 1962, Nakayama *et al.*⁴⁹ introduced an anastomotic device consisting of two metallic rings and interlocking pins that remain *in situ* as a permanent implant. The Unilink system developed by Östrup and Berggren in 1986,⁵⁰ the 3M and ACE coupling devices that were adaptations of this ring-pin device, is currently marketed under the name Microvascular Anastomotic System. This system consists of two disposable rings made of high-density polyethylene with a series of six to eight evenly spaced 0.16-mm diameter stainless steel pins that are implanted with a reusable anastomotic instrument.

The ring-pin device is a simple, efficacious, and faster technique of anastomosis and has the added advantage of not disturbing the intima in the anastomosis. It is the most successful and commonly used coaptation device. It has yielded excellent patency rates of up to 100%, even in fields that have been previously irradiated.⁵¹⁻⁵³ The rings come in a variety of sizes from 1 to 4 mm in diameter, allowing the coaptation of vessels ranging from 0.8–4.5 mm with a maximal wall thickness of 0.5 mm, and the device is suitable for both end-to-end and end-to-side anastomosis. It is contraindicated in peripheral vascular disease, areas with ongoing radiation therapy, active infection, concurrent diabetes, and corticosteroid therapy.

In an experimental comparison of venous anastomosis with use of this device, the sleeve technique, and the standard end-to-end technique, patency rates were 100%, 80%, and 95%, respectively. In an analysis of 1000 consecutive venous anastomoses with this method in breast reconstruction, Jandali *et al.*⁵⁴ reported an anastomotic time of 2–6 minutes with a 99.4% patency rate. No total flap losses were encountered. It has also been used effectively in end-to-side anastomosis of veins in head and neck free-flap reconstruction, with 99–100% patency.^{53,55} To resolve the problems of a permanent rigid ring, an absorbable anastomotic coupler was developed and has been used experimentally and clinically, achieving patency rates of 92.9–100%⁵⁶⁻⁵⁸ and 95%, respectively.⁵⁹ The ring was completely absorbed at 70 days to 30 weeks after anastomosis. Although used mainly for venous anastomoses, the mechanical coupling device has been also used successfully in performing arterial anastomoses, with up to 100% patency rate,⁶⁰⁻⁶³ proving to be expeditious, safe, and reliable. Contraindications of using this device on arterial anastomosis include thick-walled vessels that do not adequately evert, diameter discrepancies of more than 1.5:1 ratio, nonpliable vessels stiffened by prior radiotherapy or calcification, and any artery less than 1.5 mm in diameter.⁶⁰

The nonpenetrating microvascular stapler, available as a disposable device (VCS clip applier system), reported by Kirsch *et al.*,⁶⁴ uses nonpenetrating titanium clips applied in an interrupted, everting fashion. The clips come in four sizes, ranging from 0.9 to 3.0 mm, and demonstrate a reduced anastomotic time and higher patency rate. In an end-to-end anastomosis, two stay sutures are first placed at 180° to facilitate the eversion of vessel walls during clip placement and a special everting forceps and experienced assistant are needed. In an end-to-side anastomosis, four sutures are recommended with sutures at the heel and toe and two stay sutures at the 3 and 9 o'clock positions. Yamamoto *et al.*⁶⁵ reported clinical use of these staples with a mean anastomosis time of 12 minutes and Cope *et al.*⁶⁶ reported a 100% patency rate of 153 anastomoses of both veins and arteries. A comparative scanning electron microscopic study demonstrated no major differences between sutured and stapled anastomoses.⁶⁷

All anastomotic devices are essentially for use on healthy vessels only; the veins should be pliable, the arteries soft to allow eversion,⁵² and the vessel ends minimally size-discrepant.

Other nonsuture methods

Methods to glue or to weld a union of two vessels seem attractive and have been intensively studied experimentally.

Two adhesives have been studied for use in anastomoses: fibrin glues, and cyanoacrylate glues. To prevent the glue entering the vessel lumen, it was essential first to approximate the vessel walls with conventional sutures, thereby reducing the total number of sutures required for an adequate seal. Fibrin glue is now commercially available as two components, one with fibrinogen, factor XIII, and plasma proteins and a second with thrombin, aprotinin, and calcium chloride. When mixed together, it imitates the final pathway in coagulation. Fibrin glue has been used to seal anastomoses, both experimentally⁶⁸ and clinically.^{69,70} In a comparative study of fibrin glue in free flaps,⁷¹ the application of fibrin glue reduced the number of sutures required to complete the anastomosis and significantly reduced the anastomotic, but not ischemic, times with a slightly lower survival rate in the suture-only group. Although these demonstrate a faster union without compromising patency rate,^{70,71} fibrin has not achieved clinical popularity, partly because of concerns that glue might inadvertently enter the vessel lumen, and the potential for allergic reactions and anaphylaxis.⁷²⁻⁷⁴ Cyanoacrylates have been used experimentally, but have been plagued by findings of histotoxicity,⁷⁵ marked foreign-body granulomatous response, extreme thinning of the vessel wall, splitting of the elastic lamina, and calcification of the media.^{76,77} 2-Octyl-cyanoacrylate, however, might be less toxic.^{78,79}

Welding with thermal^{80,81} or laser⁸² energy has long been advocated but, despite intensive experimental investigation, its clinical application remains scarce. There are no clinical reports of thermal welding to date. Different laser types (neodymium:yttrium-aluminum-garnet,⁸² carbon dioxide,^{83,84} argon and, most recently, diode lasers^{85,86}) have been used, showing up to 100% patency rates and better blood flow in veins when compared to conventional suturing techniques. Laser-activated protein solders have been introduced to achieve more strength.⁸⁷ In an experimental setting, a diode laser-assisted carotid artery end-to-end microanastomosis provided an equal survival rate as a contralateral suture anastomosis, with a shorter anastomosis time, and scanning electron microscopy showed faster healing on the laser side.^{86,88} Although later studies have shown promising results on tensile strength, the fear of possible weakening at the site of the anastomosis with consequent pseudoaneurysm formation has so far prevented the clinical use of laser welding. In a study of 27 patients with laser-assisted microvascular anastomosis, there was a 96.6% overall success rate with one rupture of the arterial anastomosis and three hematomas requiring surgical evacuation.⁸⁹

Other experimentally studied methods of anastomosis have included cylindrical or T-shaped intravascular stents.^{90,91} An external metallic ring has been suggested to keep the cylindrical form of a sutured anastomosis and to avoid through-stitching.⁹²⁻⁹⁴

perform 100%-patent microanastomoses is the first step on the road to becoming a competent microsurgeon.

The working environment

The prerequisites of good microsurgical work are a calm disposition and patience. The surgeon must be able to concentrate on the procedure without unnecessary interruptions and should not be hurried. It is inadvisable to work too long at a stretch and it is perfectly justifiable to take a break during long sessions under the microscope or when using surgical loupes. Undoubtedly, the presence of a competent assistant and a knowledgeable specialized scrub nurse makes a big difference to the speed and ease of the operation. However, it is not uncommon for microsurgeons to operate late at night, alone, or on challenging vessels. Therefore, endurance and perseverance are virtues.

Training

"Some are born microsurgeons while others become so through discipline and training."

Because of the inherent complexity and the increased dexterity and hand-eye coordination required, the traditional apprenticeship model of surgical training cannot be as readily applied to microsurgery; and a special microsurgery apprenticeship in the form of fellowship becomes a must.

Although trainees can learn the techniques from senior surgeons in a clinical setting, training should ideally begin in the laboratory,^{95,96} with novices starting by familiarizing themselves with instrument handling under magnification, progressing from suturing stretched surgical gloves⁹⁷ or silicone tubes⁹⁸ and then to live anastomoses in a rat model.⁹⁹⁻¹⁰² Then in the clinical setting, trainees are usually given the opportunity to do the second vein first, and after achieving a steady patency, the arterial anastomosis can be handed to them under supervision. It is only when they can do both the vein and the artery well under supervision over multiple times that they can be left on their own. Challenging conditions are left to the more experienced members of the team.

Planning and positioning

In surgery, time spent planning and positioning is never wasted and this is especially true for microsurgery. In the right position, movements will be easier and the procedure will progress faster. It is important to be comfortable as comfort often relates directly to success,³⁷ while poor planning and positioning result in fatigue, frustration, and even failure.

Choosing the right incisions and the right positioning of the patient becomes easier with experience. A two-team approach can reduce the operating time and proper patient positioning alleviates the need to reposition the patient during surgery.

The surgeon should position him- or herself comfortably. If seated, preferably on a self-adjustable stool, legs should be under the operating table with feet flat on the ground. This provides a stable base that can be maintained for prolonged periods of time. The forearms should rest on folded drapes such that they are approximately at the same level as the anastomosis. These small details will minimize tremor and fatigue.

General principles of microvascular surgery

Success in microvascular surgery is multifactorial. Of the many factors attributed with success, technical skills in vessel anastomosis are a must-have craft, and learning how to

Next the microscope should be positioned so that it does not obstruct movement, while providing maximum control and maneuverability. However, the location of the anastomosis often dictates where the microscope is ultimately placed. The microscope base is then fixed to allow the surgeon sufficient room to maneuver the microscope into the exact position.

Securing the flap or flap inset

The inset of the flap should be considered before the anastomosis is performed. After circulation is restored, the flap swells and bleeds from the edges and this can make inseting the flap in deep recesses particularly difficult. This is especially true in head and neck surgery where the flap may be required in tight, hard-to-reach areas with limited visibility. The inset should be performed first, ensuring that good hemostasis has been achieved before the pedicle is divided after flap harvest. Partial or complete inset of the flap before the anastomosis also allows for a more accurate judgment of pedicle length, avoiding problems resulting from tension or redundancy. Tailoring or thinning the flap, however, is better performed while the flap is perfused either before pedicle division or after the microanastomoses to allow better control of bleeders and avoid hematoma. In some cases, such as in breast surgery, where the anastomosis lies deep to the inset, there is no choice but to inset the flap after the anastomosis is completed. In such instances, the flap is just secured near the defect, allowing adequate exposure and positioning of the vessels.

Selection and dissection of recipient vessels

Another important factor in ensuring success of free-flap surgery is the use of healthy recipient vessels of appropriate size with good outflow. Ideally they should be away from zones of trauma and sites of irradiation. A healthy vessel has a soft wall and a vascular sheath that can be easily dissected, while traumatized vessels may be encased in fibrotic tissue which is prone to bleeding during dissection. It is sometimes necessary to assess the presence and quality of the recipient vessels, particularly following irradiation and stiff neck phenomenon, lower extremity trauma or in patients with long-standing diabetes or atherosclerotic disease before flap harvest. Preoperative angiography is indicated whenever in doubt regarding the availability or quality of recipient vessels; for instance, if one or both pedal pulses are not palpable or audible by Doppler in the setting of previous trauma. However, it might not add relevant information if at least one pedal pulse is palpable,¹⁰³ and normal findings may not always translate into healthy usable vessels.

For free flaps to the extremity, clinical suspicion of vessel damage, ankle/brachial pressure index, systolic toe pressure, and hand-held Doppler auscultation may determine the need for formal angiography. Other considerations in deciding which recipient vessels to use include a single-vessel leg, multiple previous free flaps, and the availability and adequacy of recipient veins.

In head and neck reconstruction, multiple free flap reconstruction, irradiation along with frozen neck, severe atherosclerosis with peripheral artery disease, complicated osteoradionecrosis may all justify further angiographic studies.

Once the recipient vessel has been adequately exposed and identified, dissection of the vascular pedicle proceeds under loupe magnification to free sufficient length to allow a tension-free anastomosis. The total length of dissection ultimately depends upon the length of the chosen flap's pedicle, depth at which the recipient vessels are situated, the size of the vessels, and the technique of anastomosis to be used. Vein grafts have been shown to reduce success rates and can usually be avoided if proper preoperative planning has been made. If the recipient vessels are deep, for example the internal thoracic vessels in breast reconstruction, a greater length of vessel needs to be dissected in order to orientate them in a more desirable position or even more superficially to allow an unobstructed view that will facilitate the anastomosis (Fig. 24.1). Gross trimming of the adventitia is performed around the area of the anastomosis, allowing sufficient length of trimmed vessel for application of the vascular clamp. The

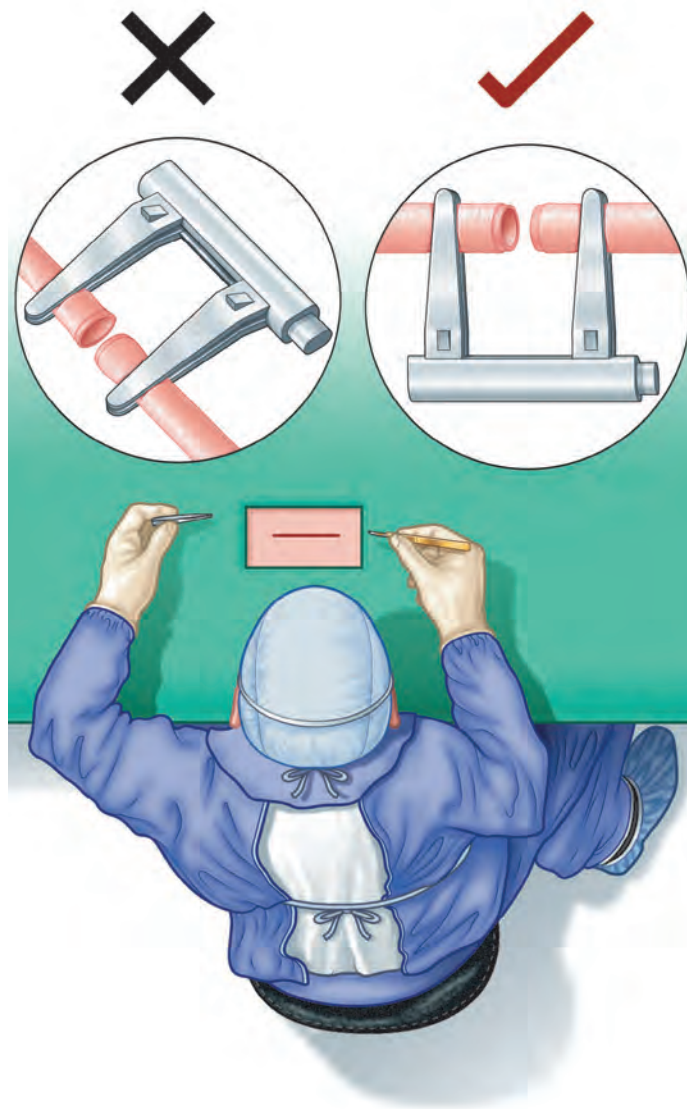


Fig. 24.1 Horizontal vessel orientation allows both lumens of the vessel to be adequately visualized.

quality of the artery and vein must then be checked. Under microscope magnification, the vessels are inspected for signs of damage that indicate the need for more proximal dissection.

It is vital to check the flow within the artery. Expansile pulsation of the vessel usually indicates adequacy but should be confirmed by healthy spurting from the divided vessel. If a healthy-looking vessel does not spurt well, check that the patient is normotensive. Steps to relieve vasospasm should be taken and are discussed later in this chapter. If there is still no relief, the vessel should be cut back until healthy spurting is encountered. Once this is confirmed, a vascular clip can be applied while waiting for the flap to be harvested or to be inset.

The ideal recipient vein should be at least as wide as the flap vein. If the recipient vein is smaller in diameter, it may produce a bottle-neck effect and compromise drainage of the flap. The vein is divided to assess its quality and good backflow from the vein indicates a fairly healthy vessel. If there is any doubt, a small catheter may be introduced into the lumen and heparinized saline flushed into the vein. If there is little or no resistance, the vein is likely to drain well. If high pressure is required to flush the vein, tying off tributaries near the site of anastomosis may help reduce the backflow. A single or double clamp is then applied in preparation for anastomosis.

The vessels should be irrigated during and after dissection with heparinized saline and, on completion of the dissection, it is common practice to cover the vessels with 2–4% lidocaine or 3% papaverine-soaked gauze pieces to prevent desiccation and vasospasm.

When the flap is ready for revascularization, the vessel ends to be anastomosed are placed in a double approximating clamp under microscope magnification. An appropriate-sized clamp is chosen to allow an adequate length from both vessels between the two clamps. This allows the vessels to be manipulated so that the lumen and intima of both can be clearly visualized whilst allowing the needle to be easily maneuvered. Moist gauze placed beneath the vessel setup is a useful way to elevate the plane of anastomosis and orientate the vessels into a horizontal lie to aid the anastomosis. It also serves as a wick to mop up any pooling fluids that may hinder the anastomosis. And, a silastic tube attached to a suction system and introduced to the microanastomosis site covered with moist gauze can further facilitate drainage without the risk of sucking the anastomosed vessels. Pliable nonadherent and nonreflective background material is placed under the vessels and clamps. If the clamps will not lie flat, a moist gauze piece is usually sufficient to weigh them down and keep them in position. Four moistened gauze pieces are placed around the vessel and clamp to prevent the suture from adhering to surrounding structures. Good hemostasis should be maintained at all times. Even a small but constant trickle of blood will obstruct the working field, decrease flap perfusion,¹⁰⁴ and potentially results in spasm and causes thrombus formation and anastomotic failure.

Preparation of vessels

The lumens of the vessels must be inspected for irregularities such as intimal tears or separation from the media, thrombi, atherosclerotic plaques, and friable calcified walls (Fig. 24.2).

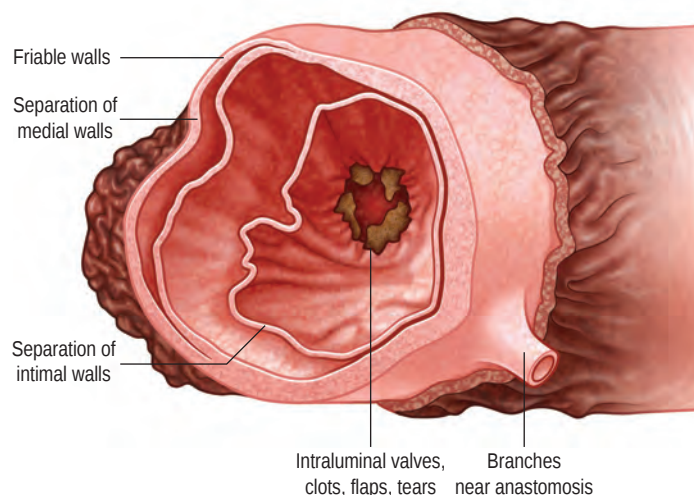


Fig. 24.2 Loose intima.

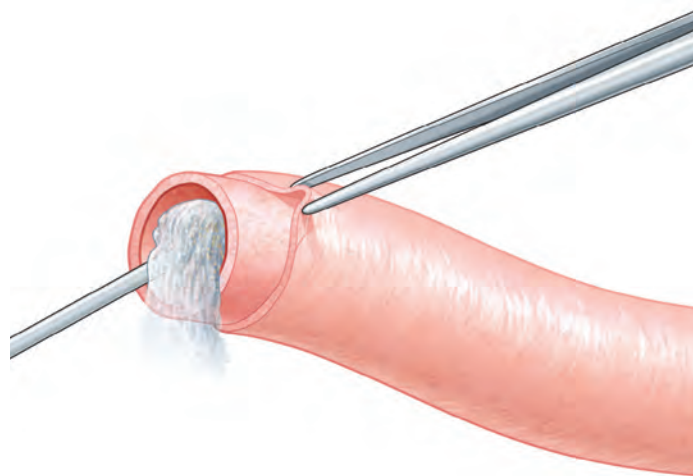


Fig. 24.3 Intraluminal irrigation of vessels.

Any debris is gently irrigated away (Fig. 24.3) or atraumatically removed with microforceps. Failing this, the vessel should be cut back, without compromising the flap pedicle length, to attain a healthier vessel segment. Occasionally, a suboptimal vessel intima has to be accepted and a successful outcome is then dependent on meticulous anastomotic technique. Some surgeons will choose to cut the vessel back to a healthy level at the expense of length, opting to use an interpositional vein graft in such situations since inadequate debridement of vessels is often a major cause of flap failure.

The vessel wall consists of three principal layers. The innermost tunica intima is formed by a single layer of endothelium resting on a basal lamina. External to this is a thin subendothelial layer consisting of connective tissue adjacent to the internal elastic lamina that separates the tunica intima from the tunica media. The tunica media consists mainly of smooth-muscle cells and is the thickest layer of the arterial wall. In veins, however, this layer is much thinner and, sometimes in lesser veins, almost indistinguishable. The tunica media is covered by the external elastic membrane, and the outermost layer of the vessel wall is the tunica

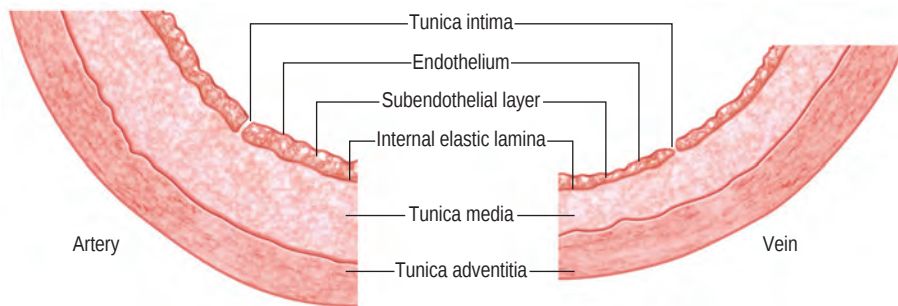


Fig. 24.4 Cross-sectional view of artery (left) and vein (right).

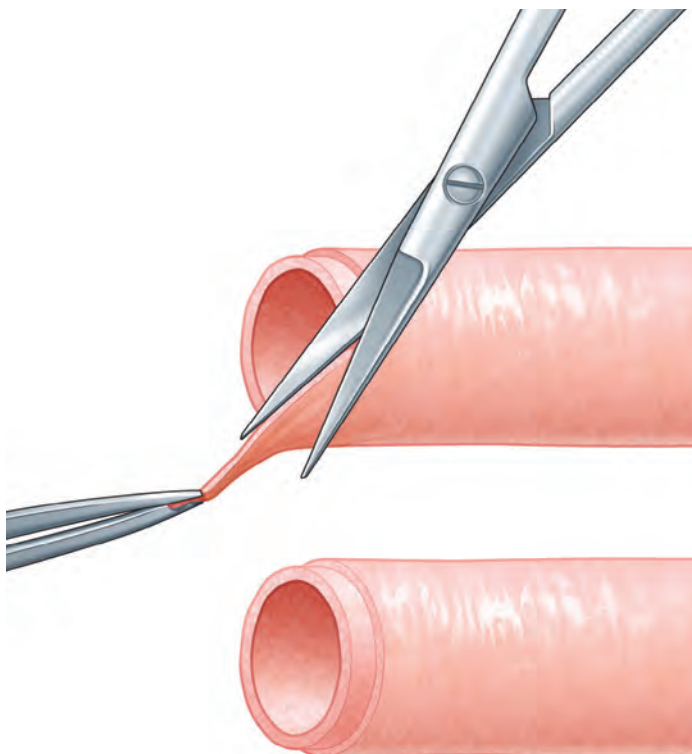


Fig. 24.5 Sharp trimming of adventitia.

adventitia. This comprises loose areolar connective tissue that contains the vasa vasorum, which nourishes the vessel wall.¹⁰⁵ Veins consist of the same layers as arteries, but the layers are less defined, particularly with regard to the tunica media which in some lesser veins is almost indistinguishable (Fig. 24.4).

Loose adventitia can be peeled off the vessel wall using microforceps or sharply trimmed by pulling it towards the lumen and cutting parallel to the luminal edge (Fig. 24.5) to a distance of 3–4 mm from the anastomotic site. It has been shown that neither method completely removes all the adventitia and that sharp dissection appears to cause less damage to the vessel.^{106,107} The main purpose is to improve visualization of the vessel ends and prevent the adventitia from falling into the lumen while tying the knot. Alternatively, a more radical trimming is performed by cutting the tented adventitia parallel to the length of the vessel, meticulously avoiding injuring the tunica media (Fig. 24.6). Avoid overly aggressive adventitial stripping as this may cause necrosis of the vessel wall at the anastomotic site with resultant false aneurysms. In

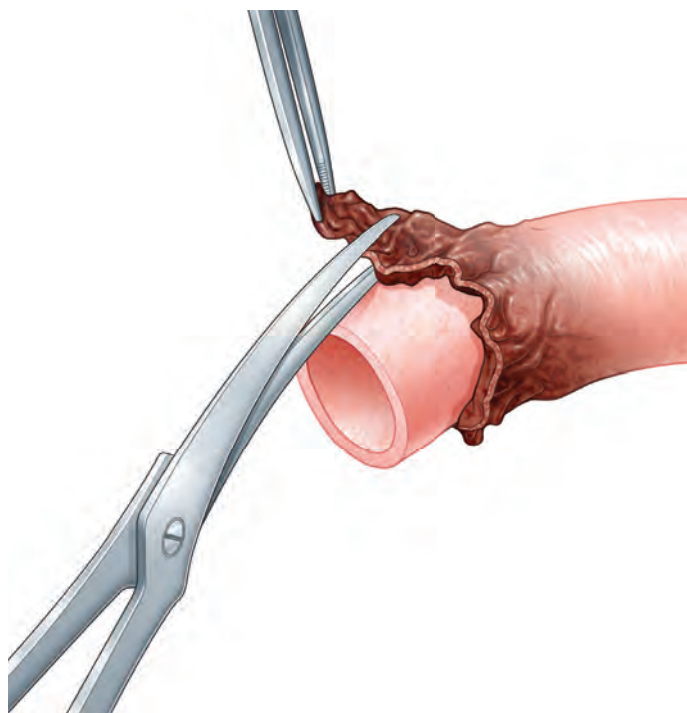


Fig. 24.6 More radical resection of adventitia.

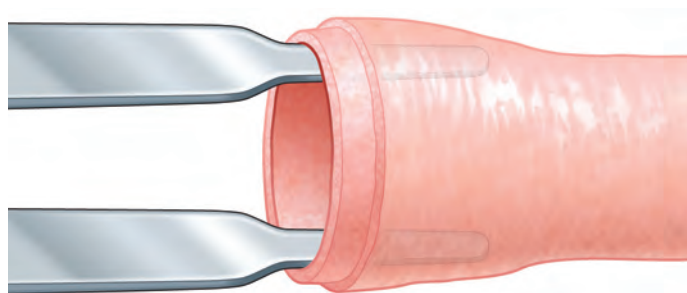


Fig. 24.7 Gentle luminal dilatation of the vessel end.

smaller veins with thin tunica media, it is advisable to remove only the adventitia that overhangs the vessel ends.

The vessel lumens are gently dilated in two different planes with a vessel dilator or microneedle holder and the stretch maintained for a second (Fig. 24.7). This will aid the suturing process, prevent vasospasm, and allow intraluminal blood to

be flushed out with heparinized saline, and overcome minor degrees of size discrepancy. Blood beyond the clamps, in undamaged vessels, is not in contact with wound thromboplastins and is not at risk of clotting. A hemostat artery forceps is used to bring the two clamps towards each other so that the vessel ends are just touching or with minimal overlap (Fig. 24.8).

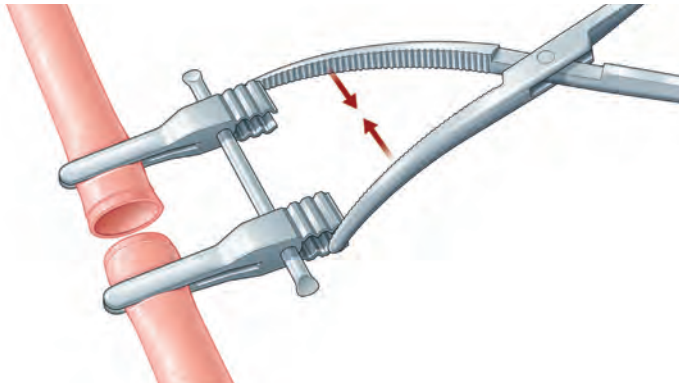


Fig. 24.8 Using artery forceps to bring the clamps together.

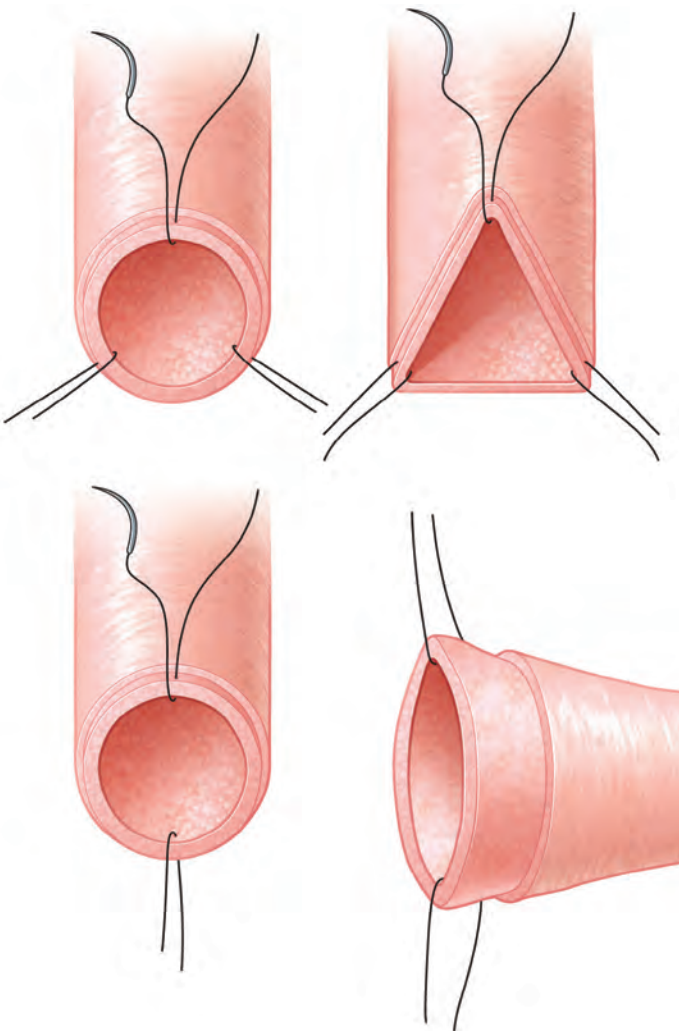


Fig. 24.9 Interrupted suturing techniques by placement of three stay sutures at 120° or at 180° to ease subsequent placement of sutures.

Anastomotic sequence

There is no consensus regarding optimal anastomotic sequence. In reality, the relative vessel position will dictate whether the artery or vein is first anastomosed, with the deeper, more-difficult-to-reach vessel being repaired first.

If the anatomy does not restrict the choice, arterial repair first may be a sensible choice as it will shorten the warm ischemia time. The re-establishment of circulation may also reveal the more dominant venous drainage to aid the selection of which donor vein to use and more importantly to detect any possible twist, kink, or compression in the pedicle, in particular the perforator. There are disadvantages, however, as the flap may start bleeding and affect the anastomosis of the vein. Subsequent venous congestion may increase bleeding from the flap edges and allow a buildup of free radicals. To avoid this, the second vein may be intermittently released to allow drainage of the flap. Alternatively, the venous anastomosis could be performed first, which additionally allows for better adjustment of the pedicle length, although this will delay revascularization of the flap.

An early experimental study showed that flap failure in straightforward cases was highest if the arterial anastomosis was performed first and immediately unclamped. This was attributed to venous congestion.¹⁰⁸ However, other studies have failed to show an optimal sequence of anastomosis in both skin and muscle flaps.^{109,110} In our practice of more than 1000 free flaps per year, we routinely repair the artery first and leave it unclamped as the vein is being repaired and have not noticed major problems related to the temporary venous congestion. If there is a second comitant vein, however, we avoid venous congestion by allowing the less dominant vein to drain freely into gauze away from the operating field.

Some surgeons advocate two venous anastomoses where possible to avoid complications of venous insufficiency, and Khouri *et al.* reported a significantly higher failure rate when only one venous anastomosis was performed (4.3% versus 0% if two anastomoses).¹¹¹ A single venous anastomosis to a suitable recipient vein however will provide adequate drainage and reduce operative time without increasing morbidity. Futran and Stack showed equivalency of single and dual venous anastomosis with respect to flap survival in a series of 43 free radial forearm flaps.¹¹² This too is our clinical experience. Sound judgment is required and, if the first vein is less reliable or if its patency is uncertain, a second venous anastomosis should be performed to secure venous drainage of the flap.

Microvascular anastomosis techniques

Having discussed the general principles of setup, vessel preparation, and common pitfalls, this section now focuses on how these principles can be applied to the different anastomotic techniques to achieve success.

Suturing techniques

End-to-end anastomosis

The method of performing the anastomosis depends largely on personal preference. The end-to-end anastomosis using

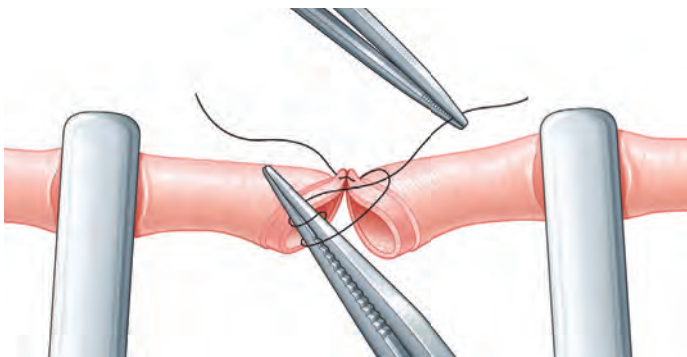


Fig. 24.10 Knot tying with a double throw.

interrupted sutures is by far the most common method used. It is simple and appropriate for most arterial and venous anastomoses. A halving, triangulation, or “back wall-up” technique can be used to perform this anastomosis (Fig. 24.9).

Carrel recommended avoiding luminal narrowing at the anastomotic site, avoiding the creation of folds and a rough inner surface of the vessel, and opposing the two intimal edges closely. These principles still hold true today. In his original description,¹¹³ three stay sutures were placed at 120° from each other. Cobbett modified this, using only two stay sutures at 120° from each other, and found that, when tensioned apart, the longer back wall fell away from the shorter front wall and reduced the chance of taking a through stitch, where the intima of the posterior wall is incorporated into the suture. Another alternative to this is placing the two stay sutures at a 180° angle to ensure even spacing between the sutures.

The second stay suture is the most important, difficult one and will determine the technique. The needle should penetrate the vessel wall in perpendicular fashion incorporating all the layers of the vessel, especially the intima. The size of the bite is determined by the thickness of the wall and the suture, and should be maintained throughout the anastomosis. The first throw should be a double one to ensure that it maintains the intended tension (Fig. 24.10), and then two single throws follow to complete the knot. The knots are snugged down by sight and not by feel and should stop when the two vessel edges meet and slightly evert. If the sutures are too tight, small tears in the vessel wall may expose the subendothelium

and allow platelet aggregation and thrombus formation.¹¹⁴ Additionally, sutures that are too tight can damage the media of the arterial wall and if at least a third of the vessel wall undergoes necrosis, re-endothelialization does not occur and occlusion of the lumen invariably follows.^{115,116} Tight sutures may also narrow the anastomosis site resulting in thrombus formation.

Sutures are then placed in between the stay sutures, aiming to place the smallest number of sutures to achieve a leakproof anastomosis, and the approximator clamp is turned over. The back wall can now be sutured by either placing a suture exactly midway between the two existing stay sutures or, with experience, sutures can be accurately placed to complete the anastomosis. As the anastomosis progresses, it becomes increasingly difficult to visualize the lumen and it is advisable to leave the last few stitches untied, leaving the ends loose until the last suture is placed. These sutures are then tied in turn. It is better to leave any apparent gaps alone until the clamp is released and the vessel refills in order to prevent through stitching. If the vessel configuration does not allow the clamp to be turned over, the back wall-up technique must be employed. The first suture is placed posterocentrally and subsequent sutures are placed on either side of the first knot, working around the circumference and spacing them appropriately apart. Once the back wall is completed, the anterior wall can be sutured using the interrupted, continuous, or open-loop suture techniques (Figs. 24.11 & 24.12).

Continuous suturing is a technique suitable for minimally size-discrepant vessels larger than 2 or 3 mm and not only can significantly reduce anastomosis time by nearly half but is more hemostatic¹¹⁷ (Fig. 24.13A). However, there are problems with suture entanglement; the sutures must be placed meticulously and the final tying of the knot must be accurate to prevent purse-string constriction of the lumen. It is advisable to place two or three stay sutures, leaving one suture end long. Starting from the last stay suture, running sutures are placed at regular intervals and tied to the next stay suture. Then the needle is passed under the vessel and the double clamp turned over and suturing continued. This reduces the likelihood of creating a purse-string effect (Fig. 24.13B). With meticulous attention to detail, patency rates of 97.5–100% can be achieved^{118–120} in both veins and arteries and end-to-end and end-to-side repairs.

Open-loop suturing is a technique that combines the convenience of the continuous running suture with the

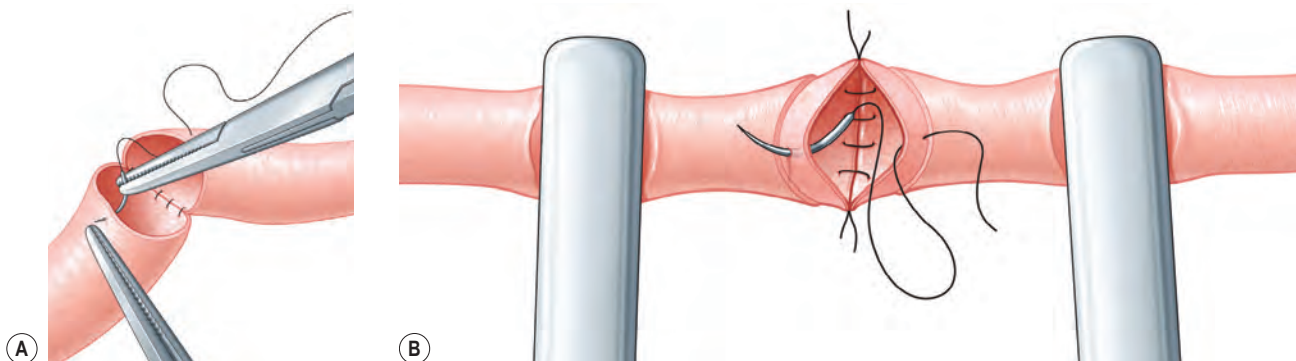


Fig. 24.11 (A, B) Placing a halving suture may facilitate accurate stitch placement when performing end-to-end anastomosis with interrupted suturing.

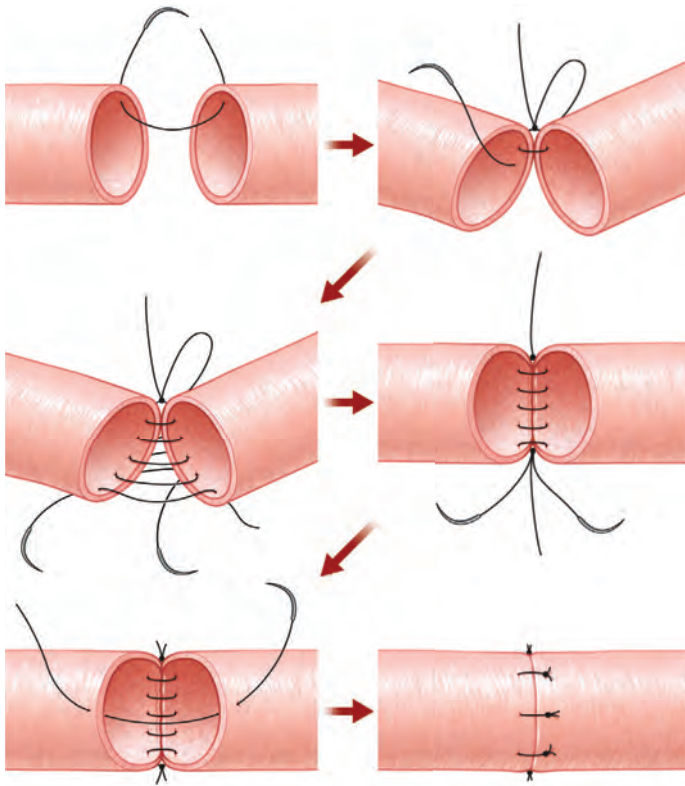


Fig. 24.12 Back wall first.

advantages of interrupted suturing technique. First a running suture is performed leaving the loops small enough that they do not flop to the side, or two separate stay stitches are placed and running suture performed in between. The first suture is tied and the suture ends cut short. The next loop is pulled through and tied in a similar fashion and cut, the maneuver repeated until all the loops have been tied (Fig. 24.14). This technique reduces the number of maneuvers and the need to handle the needle constantly after each suture. Maximal lumen visualization is maintained throughout and the risk of purse-stringing is eliminated. This method needs practice, however, as the loops can easily become entangled and time may be wasted untangling them.

Sleeve anastomosis, introduced by Lauritzen¹²¹ in 1978, is a variant of the end-to-end technique, “end-in-end”, and entails telescoping the vessels by using two extraluminal sutures that pull one vessel inside the other (Fig. 24.15). Fewer sutures are required, resulting in reduced anastomosis time and less vessel trauma, but low patency rates reported by Sully *et al.*¹²² prevented this technique from gaining popularity, despite contradictory results by others. The sleeve technique was suggested to be limited to vessels with size discrepancy. A modification of “hemi-invagination” by Riggio *et al.*¹²³ improved patency rates to 95–100% by placing a side cut on the overlapping vessel and adding a stitch at its apex, thus effectively dilating the vessel to facilitate anastomosis of vessels of equal size. However, it was only tested on rats; clinical studies are lacking.

End-to-side

The end-to-side anastomosis is particularly useful when there is significant vessel size or wall thickness discrepancy¹²⁴ or when

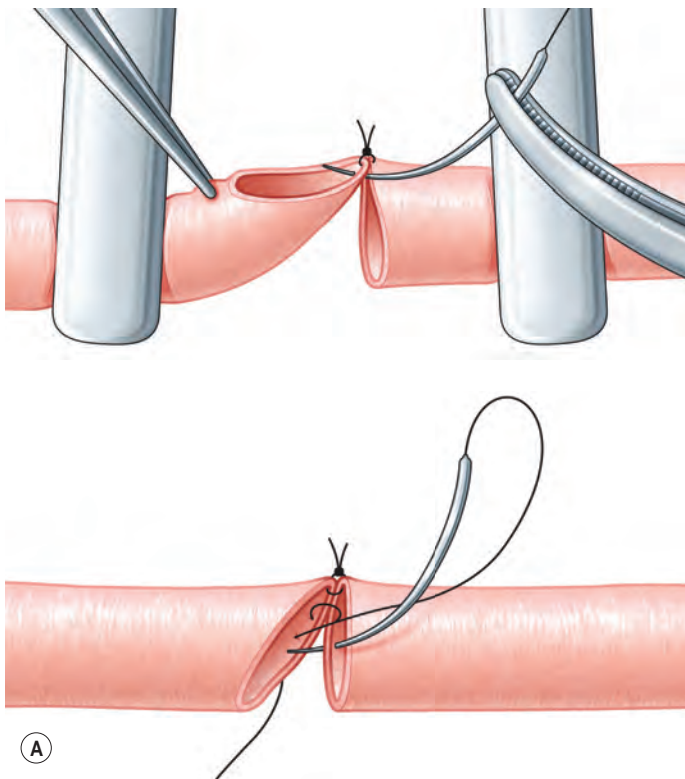
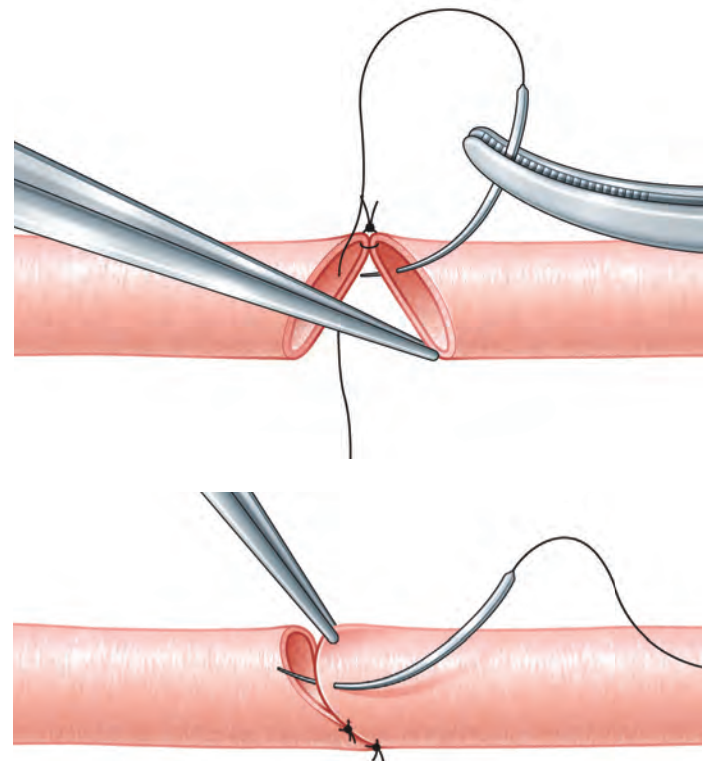


Fig. 24.13 Continuous suture. (A) Complete anastomosis using one continuous suture.



Continued

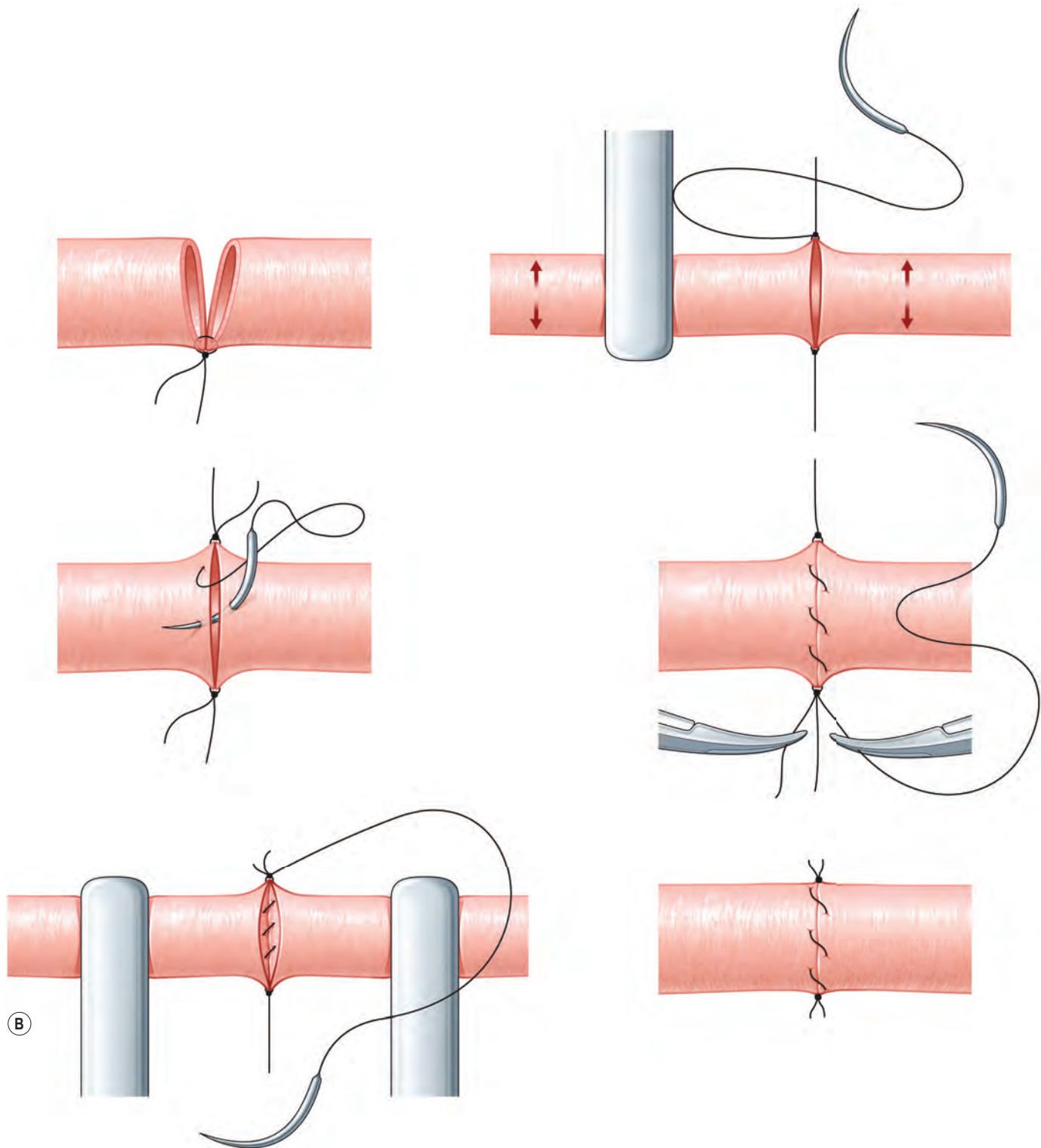


Fig. 24.13, cont'd (B) Using stay sutures placed at 180° and performing continuous sutures between the two and tying off to each stay suture prevents purse-stringing of the lumen. (From Chen YX, Chen LE, Seaber AV, Urbaniak JR. Comparison of continuous and interrupted suture techniques in microvascular anastomosis. *J Hand Surg Am.* 2001;26:530–539.)

there is a need to preserve the distal circulation, as in a single-vessel leg. Anecdotally, end-to-side anastomosis, especially, in lower extremity could be less prone to vessel spasm, associated with higher success rates,¹²⁵ but not necessarily of higher patency rates compared with end-to-end anastomosis.¹²⁶

In order to perform an end-to-side anastomosis, an arteriotomy or venotomy has to be made in the recipient vessel. This may be triangular or elliptical or a simple longitudinal slit that will open up due to contraction of the muscle in the vessel wall. The hole should not have irregular edges as this

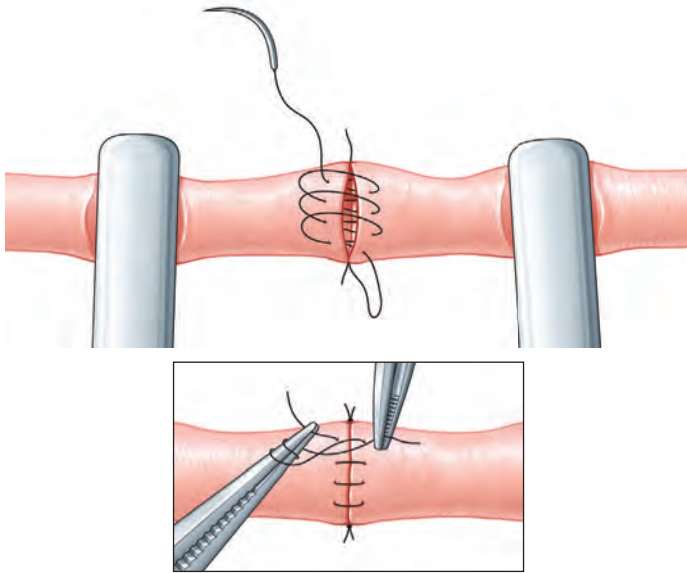


Fig. 24.14 Open-loop suture.

may weaken the wall and facilitate thrombus formation. A sufficient length of recipient vessel is dissected to allow placement of two clamps on either side of the anastomotic site and the adventitia trimmed nearly circumferentially between the two clamps. A baby Satinsky clamp is useful for clamping the recipient vessel to facilitate the anastomosis while maintaining the flow and is less traumatic than bulldog clamps. Alternatively, vascular slings may be double-looped around both ends and tightened to act as stabilizers and to cut off the blood flow to the segment of vessel. A single stitch is taken transversely at the anastomotic site and used as a stay suture. Holding this suture up, the vessel around the suture is excised using microvascular scissors and extended as necessary with a no. 11 blade (Fig. 24.16). Alternatively, the Acland–Banis arteriotomy clamp can be used to pick up and hold part of the vessel wall that is to be excised. The blade is then held close against the clamp tip, allowing an ellipse to be excised. Ideally this opening should not be longer than the diameter of the donor vessel as it will stretch once the clamps are released.

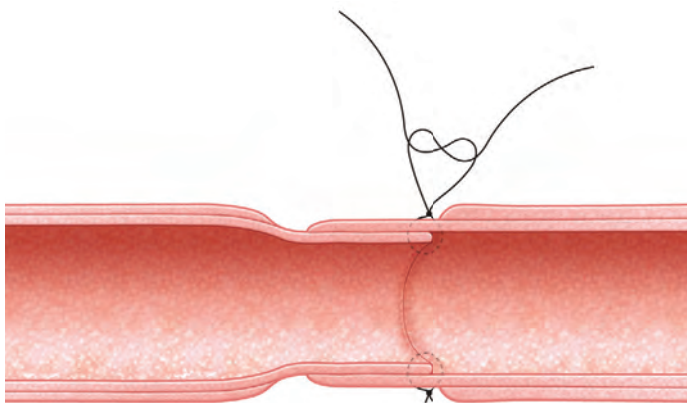


Fig. 24.15 Sleeve anastomosis.

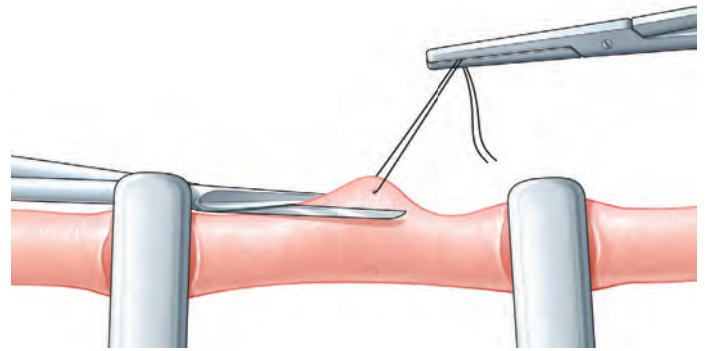


Fig. 24.16 End-to-side anastomosis. Making the arteriotomy.

If the flap vessel is long enough, the anastomosis can be performed with stay stitches at the distal and proximal ends of the arteriotomy and the “front” wall can be completed before pulling the vessel towards you and performing the “back” wall as described by Godina.¹²⁵ If there is insufficient length to manipulate the donor vessel, then the wall further from you must be performed first (Fig. 24.17). The sutures are then placed radially to the center of the arteriotomy. Persistent leakage from the distal and proximal ends may be severe if the sutures are placed transversely.

According to Godina, the additional advantages of this anastomosis included a higher success rate, greater freedom of operative planning, and technical simplicity in terms of access to the vessels and it was his anastomotic technique of choice.¹²⁵ However, in a study of over 2000 microvascular anastomoses in more than 900 tissue transplants, end-to-end and end-to-side microvascular techniques were found to be equally effective when properly applied. Patency approached 100%.¹²⁶ Although arterial anastomosis patency was similar to end-to-end anastomosis, end-to-to side venous anastomosis had a higher success rate in a study of 90 rats.¹²⁷ In a further experimental study, while there were no differences in vessel patency between an end-to-side hole and an end-to-side slit technique, the latter was easier to perform in vessels less than 1.5 mm in diameter.¹²⁸

Use of the coupler

The use of the anastomotic coupling device is the most common alternative to the conventional suture. It is a time-saving alternative that consistently produces equivalent patency rates to conventional methods. The outer diameter of each vessel is measured after gentle dilatation against the

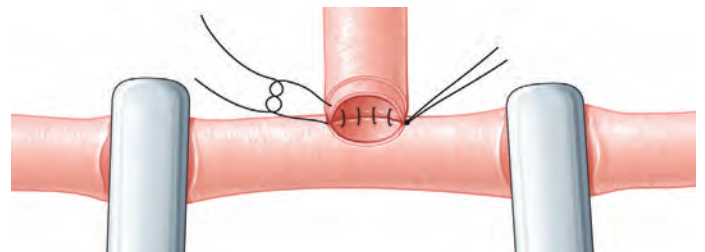


Fig. 24.17 End-to-side anastomosis. In cases where there is insufficient length to rotate the vessel, the back wall needs to be sutured first.

vessel-measuring gauge. In size-discrepant vessels, a coupler is chosen such that the internal diameter of the device is the same as the measured outer diameter of the smaller vessel.

The coupling device is loaded on to the anastomotic instrument, ensuring that it is well seated. The anastomotic instrument is placed perpendicular to the vessels, and the vessel end threaded through the ring. The edges of the vessel are impaled securely on to the first pin, taking a bite that is approximately 1–2 pin diameters with an adequate intimal bite. The vessel is impaled on every other pin first before completing the intermediate pin placements to ensure it is evenly spaced. Draping the flap vessel first allows easier position of the coupler than the less mobile recipient vessel. The rings are then brought together by turning the applicator handle clockwise and reinforced using hemostat artery forceps. The applicator handle is turned counterclockwise to eject the device (Fig. 24.18).

Difficult, less commonly encountered microvascular anastomosis

Anastomosis between size-discrepant vessels

Despite careful planning, size-discrepant vessels are commonly encountered. More problems are encountered if the inflow from the recipient is big while the flap artery is small, or if the outflow of the flap is big while the recipient vein is small, compared with the opposite conditions. It is better remembered that sudden change of caliber may still cause turbulence that predisposes to thrombosis. Various techniques are used to deal with this, and vessel mismatches of up to 4:1 can be anastomosed end-to-end depending on the level of technical skills. The simplest method is gently to stretch the smaller vessel mechanically to match the larger one, placing interrupted sutures further apart on the larger vessel. Alternatively, placing a fish-mouth incision or obliquely cutting the smaller vessel

can reduce the discrepancy. Angles of more than 30° of the oblique cut may cause kinking, and should be avoided.

Another technique involves performing the anastomosis just distal to a side branch and opening up the distal wall so that the V shape of the branch is now the vessel end. When the discrepancy is greater than 3:1, consider an end-to-side anastomosis, a vein graft to graduate the discrepancy, or using a side branch of the larger vessel, which may be a better size match. As a last resort, the smaller vessel is dilated maximally and sutured as widely as possible to the larger vessel. The remaining vessel can be directly sutured to itself and an obliquely placed surgical clip will taper the vessel and minimize turbulence (Fig. 24.19).

A discrepancy between the vessel walls may also be encountered but does not usually pose a problem. Gentle dilation will serve to thin the wall but if a significant discrepancy persists, the key is to take equal bites of the intima from both vessels, incorporating less of the media and adventitia of the thicker-walled vessel.

Vertically oriented anastomosis

This is the most challenging configuration of vessels. If possible, change the position of the body part, and adjust your position or table to make the anastomosis more horizontally oriented. Freeing up more of the vessel length will allow the vessel to be manipulated into a more horizontal plane using properly placed gauze pieces. If the position cannot be changed and there is limited space to rotate the vessel, reduce the magnification of the field as this will increase the depth of field, reducing the need to alter the focus of the microscope constantly on each vessel end.

Atherosclerosis and loose intima

Atherosclerotic vessels are commonly encountered given that free-flap surgery is extended to the elderly and those with

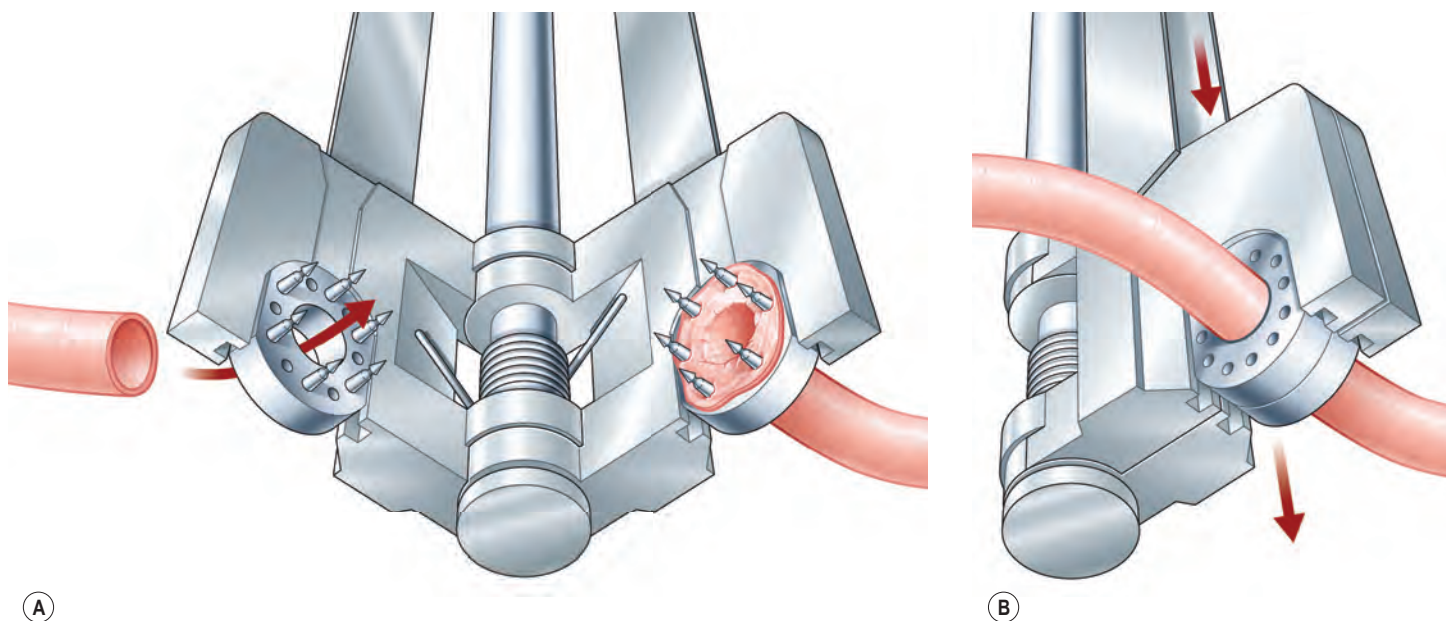


Fig. 24.18 Application of the coupler device. (A) The vessel is oriented at 90° to the applicator and the vessel end impaled evenly on the pins. (B) The vessel is anastomosed and released by turning the applicator handle.

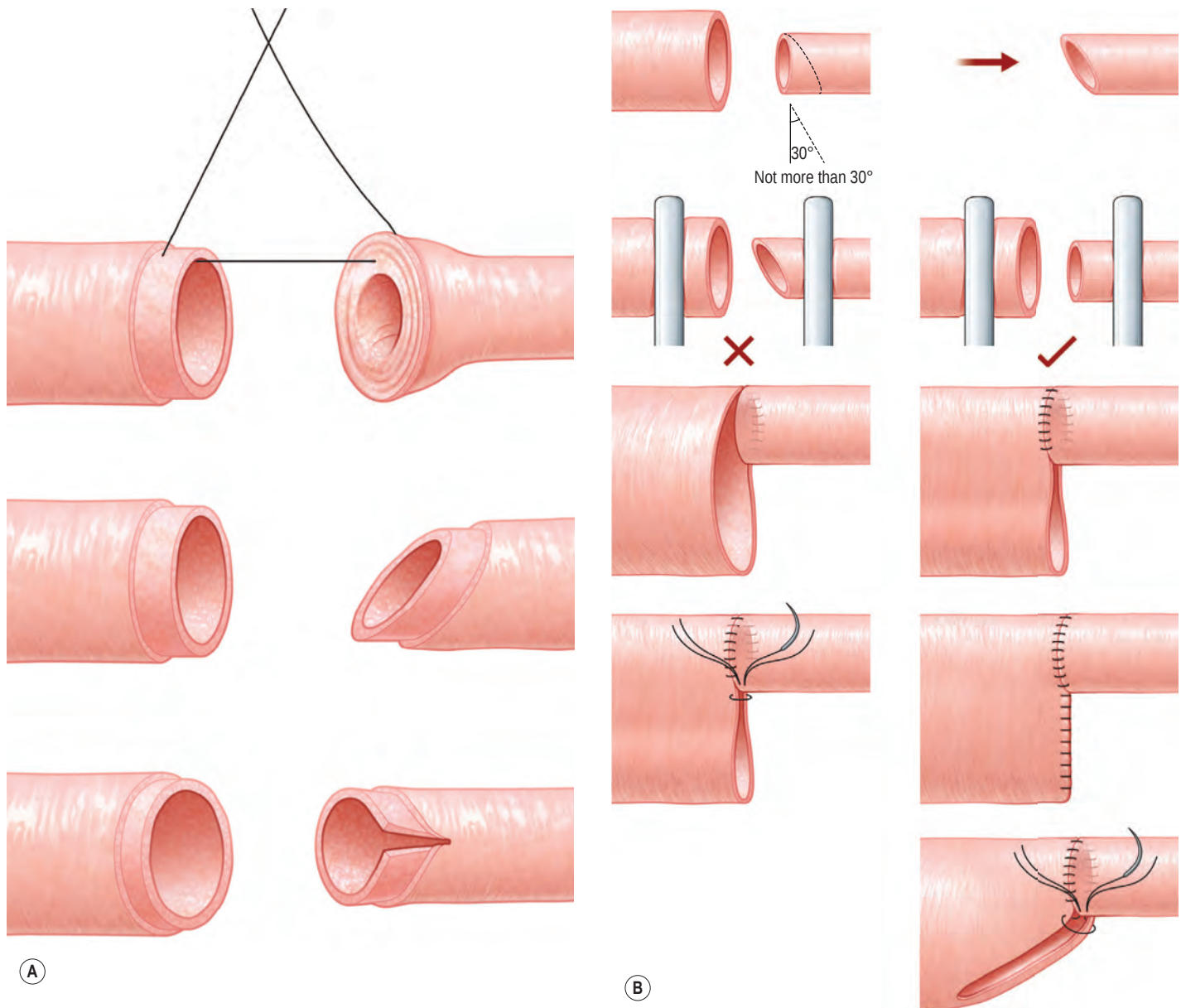


Fig. 24.19 Size-discrepant vessels. **(A)** The smaller vessel end can be dilated and stretched to match the larger one, cut obliquely to increase the diameter or a longitudinal side cut of the smaller vessel can be made. **(B)** The smaller vessel can be sutured as widely to as much of the larger vessel. A clip can be brought across obliquely to taper the remaining end of the larger vessel and may help to reduce turbulence.

cardiovascular disease. However, radiotherapy is also responsible for irradiation-induced atherosclerosis,¹²⁹ further increasing the exposure to atherosclerotic vessels in microsurgical reconstruction.

If a significant plaque is found, cutting back the vessel to healthier intima or even choosing another vessel altogether may be necessary. The artery should be divided with sharp scissors in one cut to minimize separation of the atherosclerotic intima. Sometimes atherosclerotic plaques can create a false lumen, or may appear as another vessel wall, and irregularities in these plaques can turn inside the lumen as an intraluminal flap, which may cause thrombosis. Therefore, after cutting the artery, the atherosclerotic plaque should be carefully looked for, and the cut edge should be trimmed using fine scissors. This trimming should be performed slowly

and circumferentially, in a manner resembling opening a can rather than a guillotine cut.¹³⁰

The vascular clamp should not exert too much tension as this can fracture the calcified walls or plaques. So, proper micro-clamp tension should be provided only in areas which are not affected by atherosclerosis, if used at all. One may consider microclamps which are used for venous anastomosis for both the artery and vein, so that less pressure is applied when clamping.

A round needle is useful and meticulous placement of interrupted sutures using the smallest microsuture should be ensured. The intima must be visualized at all times and the suture should ideally be passed from the inside of the lumen of the atherosclerotic vessel to the outside to avoid further separation of the intima from the vessel wall. This is possible

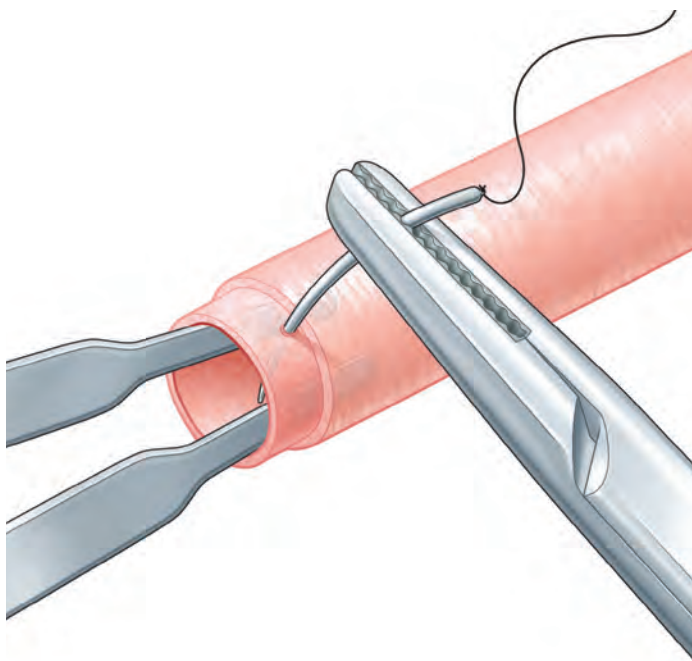


Fig. 24.20 Use of forceps to provide counterpressure to minimize trauma and separation of the intima.

if only one vessel is diseased. But when both recipient and donor are diseased, a double-needle suture may be useful. If unavailable, then careful counterpressure from forceps placed within the vessel as the needle is passed will minimize intimal separation (Fig. 24.20). Vessel dilation should be avoided and careful vessel wall eversion avoids leaving raw areas exposed to the blood flow. Too much tension, however, may erode the plaque and tear the vessel wall.

End-to-end is preferred over end-to-side that usually causes more direct exposure of the atherosclerotic plaque and its edges, resulting in increased risk of thrombus formation.

If end-to-side is unavoidable, as in single vessel-leg, an end-to-end anastomosis is used after providing a T or Y vein graft. However, vein grafts are more prone to thrombosis in these settings and the anastomosis should be finished as soon as possible because prolonged duration may increase the risk of thrombosis, causing long-term blood stasis and exposure with mechanical micro-traumas.¹³⁰

Microvascular grafts

An increased storehouse of flaps with various pedicle lengths, technical refinements, and proper planning has been key to diminishing the need for vein grafts.^{22,131} Despite this, they are still sometimes necessary, particularly in the trauma setting, vessel depleted neck, and re-explorations. There is an association between interposition vein grafting and free-flap complication and failure;^{111,132,133} however this may be a reflection of the complexity of the case and other factors such as vessel quality¹³⁴ and hematoma formation¹³⁵ that can independently lead to flap failure rather than the actual use of the vein grafts. Indeed, other studies have shown that patency and flap survival are not reduced by the use of vein grafts,^{136,137} which can be performed quickly and safely if certain principles are followed.

The indications for vein grafts include a recipient vessel out of the reach of the pedicle or under tension despite adjustments in flap inset or skeletal shortening, considerable size mismatch, and the need to place the anastomosis outside the zone of injury/radiation. Occasionally the judicious use of a Y-shaped vein graft will serve a further function of being able to restore circulation to the distal stump.¹³⁸

The harvest of the graft is just as important as the subsequent anastomosis and should be done with loupe magnification. Ideally, the vein graft should match the caliber of the vessels to be anastomosed.¹³⁹ If possible, upper limb defects are bridged with upper limb veins. The workhorse vein graft is the great/lesser saphenous vein with the advantages of length and two-team approach. Other alternatives include the cephalic and the comitant veins of the free flap. Volar forearm and dorsal foot veins are preferred in finger and hand replantation for size-match and arch-like configuration. All vein grafts need dilatation prior to anastomosis to allow a better wall thickness match. If there is a concurrent lack of soft-tissue cover, a narrow venous flap for arterial gaps may solve both problems at once.¹⁴⁰ The vein should be handled minimally during the dissection and all tributaries ligated or coagulated. The length required should be marked out, remembering that vein grafts contract after division only to lengthen considerably, with the potential risk of kinking, after restoration of high-pressure flow.

Since even short segments of veins may contain valves, the direction of the vein is crucial and must always have antegrade flow. In our practice, the proximal end is marked with a surgical clip. This facilitates hydrodilatation of the vessel which stretches the graft out to length, untwists the vein, relieves vasospasm, and allows visualization of potential bleeding points. The open end is then anastomosed first and the clamp released for a final check that the direction is correct and the length not redundant.

Arterial grafts have significant advantages over vein grafts, such as the absence of valves, an anatomical taper, similar luminal and wall-thickness profiles, and better handling characteristics. Arterial grafts maintain their endothelium and have less subintimal hyperplasia. They also produce more prostacyclin relative to vein grafts in the first 3 weeks, resulting in greater antithrombogenic activity.¹⁴¹ However they have not been shown to have significant advantages in the context of microvascular surgery.¹⁴² They may be harvested from the subscapular tree,¹⁴³ anterior and posterior interosseous arteries,¹⁴⁴ radial or ulnar arteries, the deep or superficial inferior epigastric artery,¹⁴⁵ and the dorsalis pedis artery.

Testing patency

Patency should be assessed after the completion of each anastomosis and the flap assessed for adequate perfusion periodically through the operation. This can be done by simple observation or by conducting a patency test.

The characteristics of the arterial pulsation are important and can be expansile or longitudinal. The latter occurs in the long axis of the vessel and is a sign of partial or complete thrombosis. The flap will show no evidence of return of circulation and the anastomosis should be redone. Other signs of patency of the artery include good flow from the vein. If the recipient vein fills well and has a natural round diameter it is likely to be patent. If it is engorged and the blood column

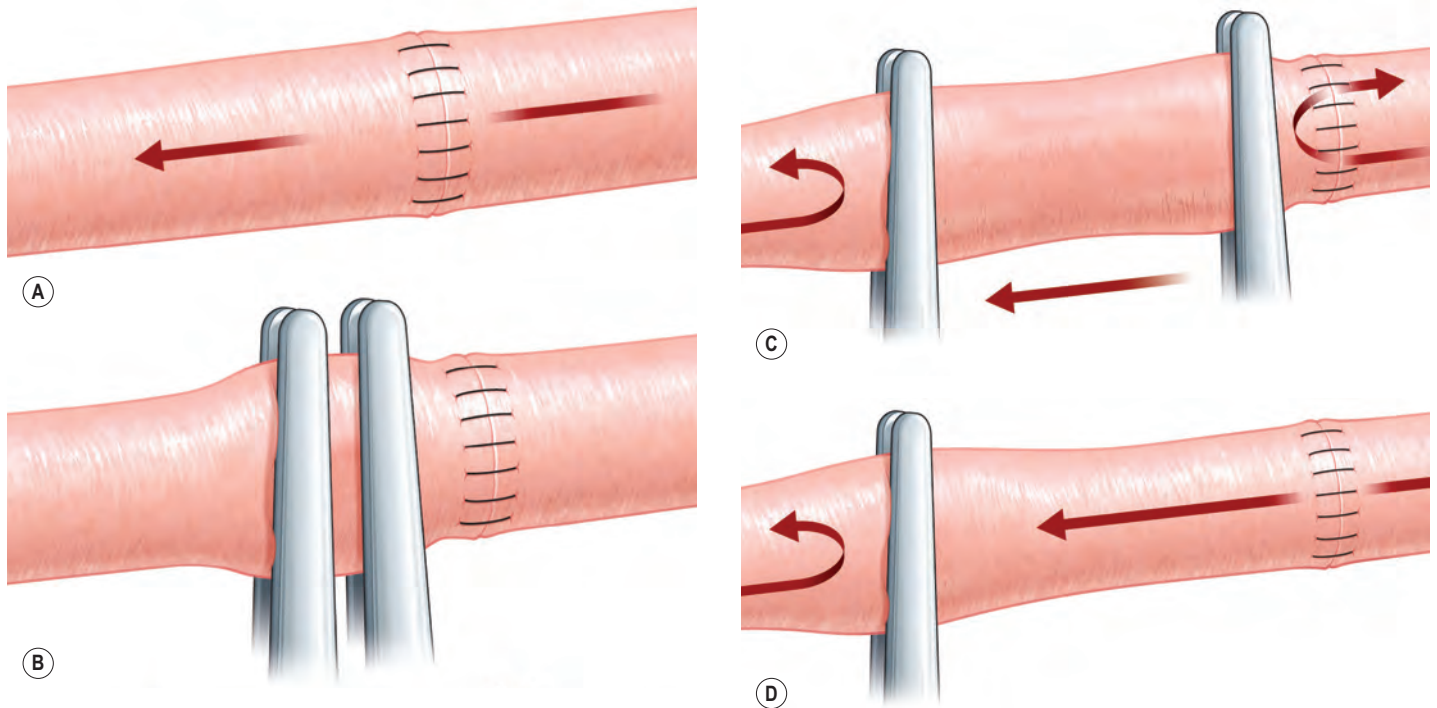


Fig. 24.21 Empty-and-refill test. (A) Direction of flow across the anastomosis. (B) Two atraumatic forceps are placed downstream of the anastomosis. (C) The forceps furthest away from the anastomosis is used to empty the vessel downstream. (D) The proximal forceps is released whilst the distal one continues to occlude the vessel. The vessel should immediately refill confirming patency.

is darker than that in the recipient vessel, it is thrombosed and will require reanastomosis. Other signs of a nonpatent venous anastomosis will include engorgement of secondary veins within the flap, and continuous dark bleeding from the edges of the flap.

If in doubt, two simple tests can be performed distal to the anastomosis. The first is an “uplift” test by gently hooking up a thin-walled vessel until the column of blood is almost occluded. If the vessel is patent, alternate filling and collapsing with each pulse will be evident. The second is the empty-and-refill test³⁷ (Fig. 24.21). This test is slightly more traumatic and should only be performed when needed, preferably on veins not arteries, to minimize spasm or intima separation. Gently occlude the vessel distal to the anastomosis, and, with a second pair of forceps, empty a segment of the vessel by occluding the vessel next to the first pair and running it in the direction of the flow. The first pair of forceps is released and the emptied segment refills immediately. If the refill is sluggish or absent, the vessel is not patent.

General aspects of free-flap surgery

Although the first clinical application of microvascular surgery was in replantation, this soon evolved into free-flap surgery, bringing about a new era in reconstructive surgery and allowing the reconstruction of previously unreconstructable defects. The concept of the reconstructive ladder and then the reconstructive elevator were introduced as a series of reconstructive options with increasing complexity; this approach to wound management has served us well for the past three decades but not anymore. With the advent of microsurgery, the aim shifts

to treatment regardless of complexity, as technical concerns become reduced. But since more complex wounds are created through more radical surgery, for either tumor extirpation or trauma debridement for which a suboptimal reconstruction is the corollary of classic methods, the best outcomes often cannot be achieved without utilizing microsurgery; this further brings on, in many occasions, single-stage total reconstruction and reverses, as a result, the reconstructive ladder/lift.

Now, it is appropriate to say that with microsurgery, the sky is the limit for reconstructive surgeons; this summarizes what we have achieved thus far and what we are going to witness years from now.

Advantages and disadvantages

The advantages of free microvascular tissue transfers over more conventional methods of reconstruction have been well documented. Free-flap surgery offers freedom of choice of donor tissue components to achieve superior functional and aesthetic results by replacing “like with like”, especially when local or regional tissue is inadequate. The flap can be tailored to meet specific requirements of the recipient site in size, form, tissue components, and even function. In contrast to regional or distant pedicled flaps that may require a multistage reconstruction, the use of free flaps is often a single-stage procedure that allows earlier mobilization and return to work, reduced hospitalization and overall costs. The new tissue has better cutaneous blood flow¹⁴⁶ and vascularity that may enhance wound healing and reduce infection. With an increasing repertoire of flaps and refinements in their harvest, a donor site which can be primarily closed with minimal donor morbidity is favored and can often be used.

When both operation and recovery proceed as planned, the advantages of free tissue transfer are clear. However, these benefits have to be weighed against the risks of long surgery and anesthesia spasm and microvascular thrombosis, re-exploration, and the dreaded complication: flap failure.

Preoperative evaluation

Patient factors

Free tissue transfer is feasible and often successful in the presence of patient factors once considered to be high-risk for flap failure. However, it is important to evaluate fully the fitness of the patient for free-flap surgery to identify and reduce the risk factors associated with poor outcome.

As with all major surgeries, cardiac and respiratory fitness should be optimized before free tissue transfer. This encompasses good preoperative hypertensive and diabetic control. Age, in itself, is not a contraindication to free-flap surgery as long as the patient is in otherwise acceptable health and deemed fit for anesthesia. The outcomes of free tissue transfer in the extremes of ages are comparable to those in the general population,^{111,147-152} although there is an increase in postoperative medical complications in the elderly.

Smoking has not been shown to significantly affect vessel patency, flap survival, and reoperation rates, but increases donor site complications with poorer wound healing at the flap-wound bed interface.¹⁵³⁻¹⁵⁶ However, patients should be advised to stop smoking preoperatively as their risk of complications approaches that of the nonsmoker if they stop smoking 4 weeks before surgery.

Obesity clearly increases the risks of microvascular surgery and is associated with increased hemorrhage and hematomas.¹¹¹ In 936 transverse rectus abdominis myocutaneous (TRAM) flap breast reconstructions, the incidence of total flap loss, hematomas, seromas, and overall donor site complications was higher in patients with a body mass index of over 30.

Alcohol withdrawal is also related to increased flap failure¹⁵⁷ and nonflap-related complications¹⁵⁸ and patients at high risk for postoperative alcohol withdrawal syndrome should be identified and treated prophylactically.

Diabetes mellitus is not an independent risk factor for flap failure, but patients with diabetes mellitus have a 1.76 increased risk of perioperative complications.¹⁵⁹

Liver cirrhosis is a risk factor for perioperative complications. Kao *et al.* showed that complications were high, but the disease severity based on Child's scoring system did not have a statistically significant impact on those complications. However, the risk of postoperative neck hematoma was significantly higher in patients with more advanced liver cirrhosis.¹⁶⁰

Immunosuppression may pose a challenge to free flap surgery. A review of 24 immunosuppressed patients found out that prednisone correlates statistically with operative morbidity, which implies that additional risks of delayed wound healing, partial flap loss, and anastomotic thrombosis should be expected in this group of patients.¹⁶¹ Patients with collagen vascular diseases such as Raynaud phenomenon, systemic lupus erythematosus, and scleroderma have increased incidence for thrombotic events such as deep vein thrombosis; however, they are not at increased risk of micro-

vascular thrombosis or flap failure as long as standard anticoagulant prophylaxis is maintained.¹⁶²

Recipients and donor site evaluation

Irradiation impairs the quality of local tissues and vessels and may predispose to complications at the recipient site.^{163,164} Khouri *et al.* found that reconstruction in an irradiated recipient site was a significant predictor of flap failure, with increased odds of failure of 4.2,¹¹¹ but many others have failed to show that radiation significantly affects flap survival.¹⁶³⁻¹⁶⁵ In our experience of 145 patients with reconstruction in an irradiated field, radiation and time between surgery and radiotherapy had no bearing on overall flap survival but increased the risk of reoperation and complications.¹⁶⁶ Careful dissection and meticulous attention to surgical technique should be undertaken when performing the anastomoses. Where possible, however, site the anastomosis outside the area of irradiation.

Infected or traumatic wounds should be adequately debrided and, if necessary, reconstructive surgery postponed until adequate control of the wound is achieved. The zone of injury needs to be taken into consideration and the anastomosis placed outside this zone where possible. Preoperative angiography or computed tomography angiogram is recommended in patients with abnormal distal pulses,¹⁶⁷ and in those in whom both pedal pulses are not palpable/audible by Doppler.¹⁰³ Normal angiographic findings do not guarantee the presence of vessels suitable for anastomosis, and routine angiography is unjustified.¹⁶⁸

Harvesting a free flap requires an intimate knowledge of the anatomy of the vessels, and their variations, supplying the transferred tissues. The design of the flap may be centered on perforators that are mapped out by a hand-held Doppler device¹⁶⁹ or more accurately through color duplex ultrasound,¹⁷⁰⁻¹⁷² computed tomography angiography with or without three-dimensional reconstruction¹⁷³⁻¹⁷⁵ or magnetic resonance imaging angiograms.¹⁷⁶⁻¹⁷⁸ Accurate preoperative mapping has been shown to aid perforator selection, increase the safety of perforator dissection, and reduce operative time.^{172,175,178}

Choice of flap

Preoperative planning and flap selection and design are more important than the harvest itself. There is no flap ideal for all circumstances and the surgeon must accept some compromises to choose the most appropriate available flap for the patient. Chosen well, the patient comes away with an optimal result; chosen badly, and the entire reconstruction is set up to fail.

The first question to answer is: "Does this defect need a free flap?" If the answer is yes, then other factors to be considered include the size and tissue components of the defect and the goals of reconstruction. For example, for a young patient with a benign tumor of the mandible, in whom functional outcome is as important as aesthetic outcome, a flap that incorporates vascularized bone for immediate or delayed osteointegration of dental implants should be chosen (Fig. 24.22). Conversely, an edentulous elderly patient with a poor-prognosis mandibular cancer and trismus may benefit from a more straightforward operation with a reconstruction plate and soft tissue flap

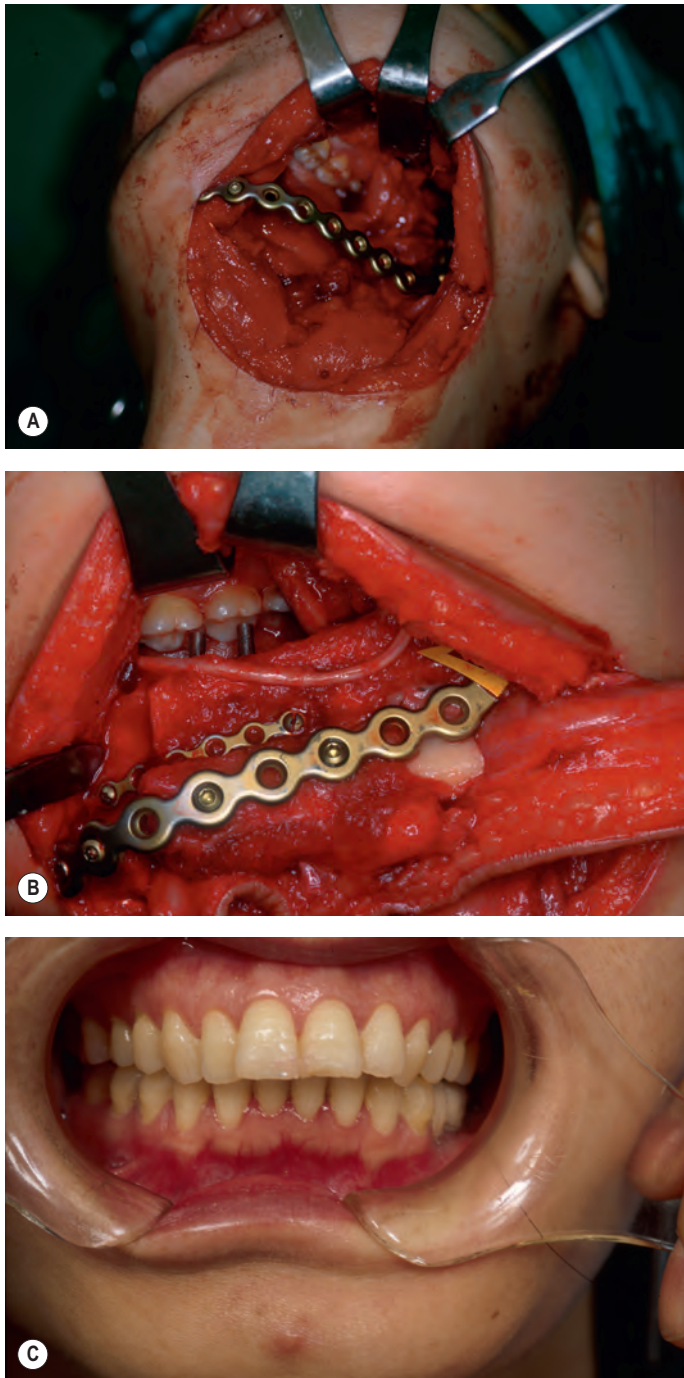


Fig. 24.22 Osteointegrated teeth in a fibula osteoseptocutaneous flap reconstructed neo-mandible. (A) Segmental defect of the mandible after tumor excision. (B) Double-barreled fibula inset. (C) Final appearance of the mandible after osteointegrated teeth implantations.

with adequate tissue volume such as the anterolateral thigh flap combined with vastus lateralis muscle that addresses the primary goal of uncomplicated wound healing. This approach reserves the potential for secondary optimal reconstruction in cases not suitable for one-stage bony reconstruction.¹⁷⁹ Appropriately sized recipient vessels must be available and must be considered in deciding the length and caliber of the flap pedicle. This may ultimately decide the suitability of one flap

over another in order to minimize the need for interpositional vein grafts.

An important consideration is the potential donor site, such as the cosmetic result of the donor site that requires skin grafting and reduced muscle power and potential herniation following muscle flap and even perforator flap harvest. Consideration should also be given to the logistics of the flap harvest, patient positioning, and the feasibility of using a two-team approach to streamline the operation.

Timing

The timing of post-traumatic lower extremity reconstruction has been the subject of ongoing debate since Godina first recommended that they be performed within 72 hours of injury.¹⁸⁰ Today, when the free flap is actually performed is largely determined by the surgeon's experience and assessment and the local healthcare system, logistics, and facilities. The definitions of the ideal time periods also vary significantly, with some defining acute reconstruction as the interval ranging from emergency or immediate procedures within 24 hours to urgent procedures done within 72 hours, and others suggesting that the first 24 hours be termed "primary free-flap closure."¹⁸¹ There are those who advocate reconstruction within 72 hours^{182,183} or 5 days,¹⁸⁴ but proponents of delaying the reconstruction argue that the viability of an extremity can be better assessed, the reconstructive procedure better planned, and performed under better operating conditions. In our practice, we have found that adequate debridement results in a fresh surgical wound that can be reconstructed at any time and that actual timing has little to do with the final outcome of the flap. However, we agree that immediate cover must be considered if vital structures are exposed and that, on occasion, emergency free-flap transfer may salvage a devascularized limb or a finger, in addition to improving the functional and aesthetic results and shortening the hospital stay.¹⁸⁵ In oncological reconstructions, immediate reconstruction is performed at the same time as the ablative surgery to achieve uncomplicated wound healing. Reconstruction at the same time has been shown to delay the delivery of adjuvant therapy modestly.¹⁸⁶ In reconstruction of the breast, if patients will receive or have already received postmastectomy radiation therapy, the optimal approach is delayed autologous tissue reconstruction after postmastectomy radiation therapy. However, when postmastectomy radiation therapy appears likely but may not be required, delayed-immediate reconstruction, in which tissue expansion is used, may be considered.¹⁸⁷ A recent multicentric study showed a surge in immediate reconstruction rate favoring implant use due to an increase in the proportion of high-risk patients undergoing immediate reconstruction. Interestingly, though, autologous free tissue transfer also increased in the high-risk group but not in the setting of premastectomy radiotherapy.¹⁸⁸

Microvascular anesthesia

The importance of stable anesthesia by an anesthetic team familiar with microsurgery should not be underestimated. Good pain, temperature, and sympathetic control should be maintained throughout to prevent vasospasm and vasoconstriction. Fine-tuning of blood pressure will help in ensuring

that the operation proceeds smoothly; during flap dissection, the blood pressure should be kept adequately low to keep a bloodless field, but brought up gradually when hemostasis is being secured and the anastomosis being performed to ensure good recipient inflow and flap perfusion. Adequate fluid management includes slight hemodilution to maintain high cardiac output and low systemic vascular resistance.¹⁸⁹

Special techniques and flap modifications

Increasing familiarity with the principles and techniques of microsurgery has encouraged various innovations and refinements in the pursuit of excellence. The goal now is not only simply to achieve closure, but to do so with the least amount of donor morbidity, in the shortest operative time, and with the best results in terms of function and appearance.

Endoscopic harvest

Endoscope-assisted harvest of free flaps allows the use of smaller incisions and improved donor site appearance. However this requires special instrumentation and a steep learning curve that may initially increase the operative time. Flaps harvested with endoscope assistance include gracilis,¹⁹⁰ rectus abdominis,¹⁹¹ and latissimus dorsi¹⁹² muscle flaps, temporoparietal fascial flaps,^{193,194} and jejunal segments.¹⁹⁵ Although the complication rates are not dissimilar, incision lengths are shorter, donor site morbidity and pain are reduced, and patient satisfaction is higher when the flaps are harvested endoscopically.

Robot-assisted free-flap surgery

The robot represents the most up-to-date technological innovation in surgery. Its platform can provide high definition 12×–15× digital magnification, broader range of motion, fine instrument handling with decreased tremor, reduced surgeon fatigue, and improved surgical productivity.^{196,197} The role it plays in urologic, gynecologic, cardiac, general, and endocrine surgery is undisputable. However, in reconstructive microsurgery, the application of robots is still preliminary, but not without potential. Transoral robotic surgeries have eliminated lip- and mandible-splitting approaches and allowed the ablation of tumors that have until recently been primarily treated non-surgically.¹⁹⁸ For the robot-created defects, a robot-assisted free tissue transfer could be safely indicated but at the price of prolonged surgery time.¹⁹⁹ Other indications are recipient vessel preparation, in particular the internal mammary vessels for free-flap breast reconstruction,²⁰⁰ and free flap harvest, and the latissimus dorsi, through minimal-access incisions.²⁰¹ Usage in brachial plexus has also been described to improve the surgery.²⁰²

Perforator flaps, free-style flaps, and supramicrosurgery

A perforator flap is defined as a flap based on a musculocutaneous perforating vessel that is directly visualized and dissected free from the surrounding muscle until adequate pedicle length and caliber are obtained (Fig. 24.23). This

minimizes donor site morbidity and allows the harvest of only the specific components required for the reconstruction. In areas where the anatomy of the cutaneous vessels has not been studied extensively or with flaps with considerable variation in anatomy of their blood supply, the detection of an audible perforator with a hand-held Doppler probe may form the basis of flap harvest.¹⁷¹ The vessel is identified at the level of the fascia, through an exploratory incision, and if sizeable (0.5 mm with good visible pulsation), then dissection in a retrograde fashion will follow its course to the parent vessel on which the flap may be raised as a free flap. This concept has been termed “free-style free flaps”²⁰³ and these flaps can be designed almost anywhere as long as small-caliber vessels and small to medium-sized skin paddles are acceptable when pedicle length is not critical.

To reduce donor site morbidity further, Koshima *et al.* advocate supramicrosurgery,^{204–206} the dissection and anastomosis of vessels with diameters of less than 1 mm. This allows flaps based on vessels harvested without breaching the deep fascia, facilitating a quick operative harvest time without intramuscular dissection, but yields a very short pedicle that requires highly honed surgical skills and extremely fine instruments and sutures.

Combined flaps

When the flap consists of diverse tissue components with multiple sources of vascularization, often discrete to each component, the flap is called combined. Based on the physical relationship between the flap components, the combined flap is subdivided into conjoined and chimeric.^{207,208} In conjoined flaps, previously known as Siamese, multiple anatomical territories are dependent due to some common physical junction yet each retains an independent vascular supply.²⁰⁸ In chimeric flaps, on the other hand, there is no physical junction between the territories, perforasomes, components, etc. The conjoined flap has the advantage of providing large surface area while the chimeric allows the freedom of placement of each component and often results in an optimal one-stage reconstruction

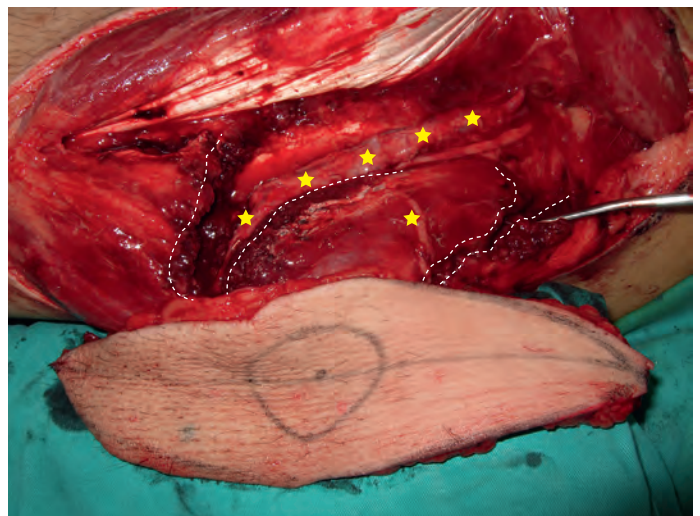


Fig. 24.23 Perforator flap harvest via an intramuscular dissection of the perforators. *Perforator. *****Source artery of the perforators: descending branch of the circumflex iliac artery. ----- Edge of the dissected vastus lateralis muscle.

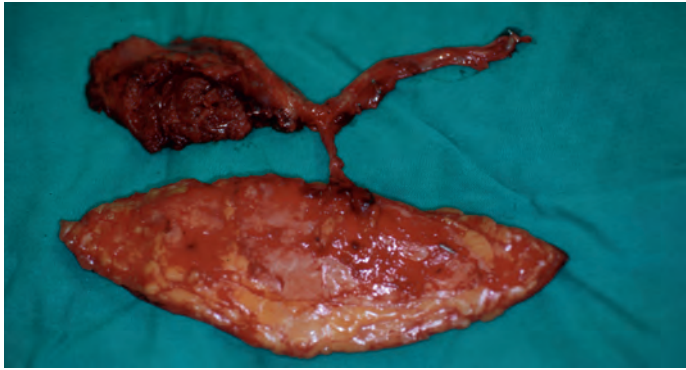


Fig. 24.24 Chimeric flap with muscle and skin component.

of compound defects^{209,210} (Fig. 24.24). Flaps that are microsur-gically fabricated or linked are a subtype of chimeric flap that allows multi-goal reconstruction,²⁰⁸ and they should be considered the “true chimera”. Finally, the concepts of conjoined and chimeric flaps are also applicable to perforator-based flaps.

Thinned flaps

Flaps that are thick and bulky often require a secondary revision in order to improve final outcome. However, with better understanding of the vascular supply and from increasing experience with perforator flaps, one-stage flap thinning has become possible. Skin is nourished by a subdermal plexus arising from branches of the main pedicle in addition to recurrent dermal branches and thinning can be performed safely to about 3–4 mm in thickness in Asians, leaving an unthinned area of 2 cm around the pedicle.²¹¹ This reduces the need for secondary revisions.²¹² Another method of thinning is micro-dissection of blood vessels in the adipose layer under micro-scopic magnification and removal of the adipose tissue surrounding the vessel^{213–215} (Fig. 24.25). The third method that appears promising but still needs further anatomic investigations for wider application throughout the body is to harvest the flap at the level of the Scarpa’s fascia with the superficial circumflex artery perforator flap being the flap of choice for this method.²¹⁶

Prefabricated/prelaminated flaps

Some defects require complex reconstructions of various components that cannot be met by conventional flaps. Flap prefabrication and prelamination have been applied to areas where specific contours and structures are desired, for example, in reconstruction of the esophagus, penis, and certain head and neck defects.

Prefabrication involves a two-stage process, the first of which implants an axial vascular pedicle into the donor tissue that is required,²¹⁷ thus allowing it to be transferable once neovascularization has occurred. The second stage, about 8 weeks after the implantation, involves the transfer of this neovascularized tissue, based on its recently implanted pedicle, to reconstruct the defect on its recently implanted pedicle. This allows the creation of large, thin skin flaps that retain the qualities of the donor site and can be modified with various combinations of vascular pedicles, donor tissues, and geographic locations for different clinical needs.^{218,219}

Prelamination is another two-stage process where one or more tissues are added to a reliable vascular bed to create a multilayered composite flap. In the second stage, once matured in approximately 2 weeks, the composite flap is transplanted to the defect. This delayed procedure allows the best chance for the prelaminating layers to heal, stabilize, and assume their expected structures and positions. By laminating the vascular bed with skin, bone, cartilage, or mucosa, prelami-nated flaps have been used to reconstruct the oral lining,²²⁰ ear,²²¹ nose,^{222,223} neourethra,²²⁴ penis,²²² and trachea and larynx.²²⁵

Postoperative management, complications, and outcomes

The postoperative management of the patient is crucial in preventing major morbidity and mortality. Patients should be kept warm, adequately hydrated (hematocrit <0.3), and pain free. Blood pressure should be normalized based on preoperative blood pressure and tachycardia avoided as sympathetic overdrive may cause vasospasm. Good hyperglycemic control reduces the incidence of complications in the surgical patient who may require insulin therapy. Prophylactic antibiotics are routinely prescribed to prevent wound infection and low-molecular-weight heparin is used to prevent deep vein thromboses.

Monitoring

Monitoring begins on the re-establishment of blood flow into the flap. The flap should constantly be assessed on release of the microvascular clamps, during closure, on completion of inset, when the patient transfers from the table, and on admission into the ward.²²⁶ Early detection and intervention of flap problems can improve overall flap salvage.^{227–229} Although many methods of flap monitoring are now available, none has been completely effective or uniformly accepted. The ideal monitor should be reliable, noninvasive, objectively repeat-able, promptly reactive to blood flow changes, appropriate for continuous monitoring in all types of free tissue transfers, usable for the unskilled, and economically available.²³⁰

There is no substitute for experienced nursing and medical staff, whether in a dedicated intensive care unit or on the general ward. Clinical observation of the flap is the gold standard for monitoring and should be performed at 30-minute

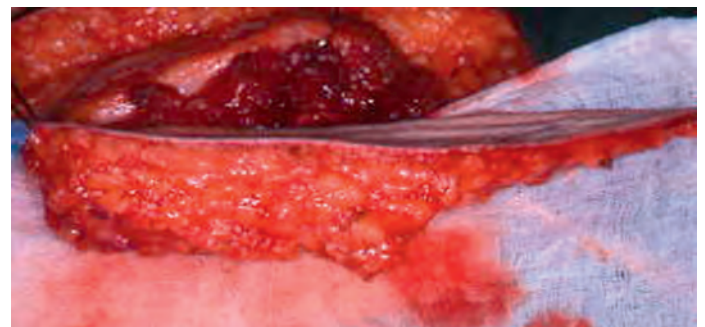


Fig. 24.25 Thinning of a thick cutaneous flap. Image shows the edge of the flap where flap has been excised safely to thin the flap according to requirements.

intervals for the first 24 hours. This can be extended to 1–2-hourly for the next 24 hours, then 4-hourly for the next 48 hours. Signs to be noted are color, capillary refill, turgor, and surface temperature. If capillary refill is not obvious, pinprick testing can be used to observe the color and speed of bleeding. However, this pinprick should just scratch the dermis and not penetrate too deeply and risk injury to the underlying pedicle. This form of monitoring may not be as suitable for flaps in aesthetically important areas. Surface temperature measurement with a surface temperature probe is easy and inexpensive²³¹ and a recorded difference of 1.8°C between flap and control sites is 98% sensitive and 75% predictive of vascular compromise.²³² The trend of the temperature of the flap over time is also a useful guide to the failing flap²²⁶ and temperatures below 30°C are indicative of flap failure.²³³

A hand-held pencil Doppler probe (low-frequency continuous ultrasonography)²³¹ applied on to the flap over a cutaneous perforator location is another method of monitoring. This point should be marked intraoperatively away from the pedicle to prevent false-positive results. An implantable Doppler probe can be used to monitor flaps without a perforator to the skin or buried flaps.²³⁴ This small probe is attached to a polymer sleeve that is placed around the pedicle vessel (most accurate on the vein) adjacent to the anastomosis with a probe lead wire exiting through the incision. This lead is removed by gentle traction which leaves the sleeve in place when monitoring is no longer required. The signals have a characteristic pattern that can differentiate arterial from venous thrombosis. The method is sensitive; however, it has a high false positive rate, resulting in frequent intraoperative maneuvers to amend the cause of signal loss. Some authors even reported on significantly more vascular thrombotic events when compared to the non-flow coupler group.²³⁵ Laser Doppler measures the reflected waveforms of light, from a helium–neon laser, by the red blood cells moving within the capillaries, and provides an objective measurement for flap perfusion. Interpretation of the results of laser Doppler requires experience but can be very accurate, detecting vascular compromise with no false positives or negatives²³⁶ and distinguishing venous obstruction from arterial occlusion.²³⁷

Other available adjuncts less commonly used include pulse oximetry to identify both a pulsatile flow and arterial saturation in replanted or revascularized digits or toe-to-hand transfers,²³⁸ photography, tissue oxygen tension measurement, tissue pH levels, microdialysis, fluorescein dye mapping, near-infrared spectroscopy, thermodilution technology, photoplethysmography, and nuclear medicine studies.²³⁹

In a recent survey of the members of American Society of Reconstructive Microsurgery, a questionnaire concerning perceptions and frequency of use of several technologies in varied clinical situations revealed that hand-held Doppler was the most commonly used technology; however, surgeons were more willing to opt for immediate take-back to the operating room based on concerning findings of tissue oximetry compared with concerning Doppler signals.²⁴⁰ This suggests that of all available adjunct technologies, tissue oximetry may have the greatest impact on clinical decision-making in the postoperative period.

Nevertheless, clinical monitoring remains the gold standard and, regardless of which adjunct is additionally used, close flap monitoring should be a standard part of the

postoperative care of these patients during the first 72 hours after surgery at the minimum.

Telemonitoring

The clinical inspection remains the gold standard in free flap monitoring; however, it necessitates that the decision-maker evaluates the flap him/herself to decide on take-back to the operating theatre or “close eye-on” approach. To enhance communication and make clinical inspection friendly yet efficient, smart phones can be used. These carry-on devices when integrated in flap monitoring showed comparable accuracy rate but shorter response time compared with in-person examination,²⁴¹ which may increase salvage rate and overall flap success rate,²⁴² making the combined use of smart phones and internet appealing and invaluable in the modern era of digital technology.

Buried flaps

Monitoring buried flaps postoperatively is a challenge and many techniques have been used to assess the flaps, either directly or indirectly. Implantable Doppler probes have been used routinely, as covered previously. However, due to high sensitivity and positive-negativity, it could now be utilized as a screening tool and a color Doppler can be used to confirm the findings or avert unnecessary surgical exploration.²⁴³ Alternatively, color Doppler ultrasound can verify normal arterial and venous flow through the pedicle, as demonstrated in a functioning muscle transfer study.²⁴⁴

Part of the flap may be externalized. For example, a jejunal stump may be brought to the surface to observe peristalsis and color or a skin paddle may be externalized. This should be used with some caution as this only monitors the common source vessel and may not accurately reflect the buried component, especially if the two components are based on different perforators.²⁴⁵ The distal end of the pedicle that is usually ligated close to the supply of the skin can also be externalized and its pulsations observed directly under a transparent film dressing. This can then be tied off in the follow-up clinic.²⁴⁶

Flap outcomes

With maturation of microsurgical technique, failures have thankfully become rarer and success rates of free tissue transfers now range from 96% to 100%.^{22,66} Failures can be attributed to poor planning, poor choice of flap or vessels, poor timing, or poor technique. However, many of the failing flaps may be salvaged and the success of the salvage (54–100%¹¹¹) is in part dependent on good patient management, highly trained staff, and early detection and intervention.

When a flap begins to fail, the likely causes must be identified and rectified. Although the majority of the complications are related to vascular compromise, simple measures should be taken by the bedside first to avoid unnecessary explorations. Systemic factors such as hypotension, hypovolemia, hypothermia, and sympathetic overdrive due to pain should be resolved. Once the blood pressure is normalized and the patient warmed up, the flap should be reassessed for the need to return to the operating room. Local factors include the release of external compression secondary to compressive surgical dressing, hematoma, or a tight wound closure. Releasing some sutures or loosening the dressings may relieve

the compression, solving the problem or at least temporizing the immediate threat to the flap before the formal salvage procedure. If the flap does not improve, a bedside exploration of the vessels can be performed to relieve vessel twist or kink, to assess the patency of the microanastomosis, and to open the pedicle second-vein to resolve ongoing congestion. After that, a prompt return to the operating room is mandatory in the evidence of thrombosis. Resection and reanastomosis or the use of a Fogarty thrombectomy²⁴⁷ may be required. Intraoperative lysis with urokinase or tissue-type plasminogen activator may also help.^{248–250}

Causes of a failing flap

Anastomotic failure

There are many causes of anastomotic failure, such as those related to technical errors in the anastomosis, or intrinsic factors predisposing to vasospasm or thrombogenesis.

The principal faults leading to anastomotic failure are tearing, leaking, narrowing of the lumen, through-stitching, and inclusion of the adventitia.³⁷ Tearing occurs when there is too much tension at the site of the repair. It can also be caused by too meticulous stripping of adventitia: the veins of the head and neck region are especially fragile. Leaking occurs when there is too big a gap between sutures, or there is a tear or a tiny unnoticed branch near the anastomotic site. Even a small leak will precipitate intraluminal thrombus formation²⁵¹ and narrowing of the lumen can also be caused by oversized bites, entangling knots with one another, or continuous suturing that is too tight. Through-stitching entails taking a bite of the back wall with the suture, causing luminal obstruction. This can be avoided by always visualizing the lumen of the vessel through constant luminal irrigation by an assistant or by raising the anterior wall with the tips of microforceps to separate it from the back wall. Inclusion of adventitia as a result of inadequate vessel preparation should be avoided as the prolapsed adventitia is another nidus for thrombus formation. Finally, desiccation of the vessel may also lead to failure.

Vasospasm

Vasospasm occurs in 5–10% of microsurgical procedures and plays an important role in the pathogenesis of hypoperfusion, promoting thrombosis, which may lead to partial or total flap loss. It may be seen intraoperatively and up to 72 hours postoperatively, with the former often being more problematic. The pathophysiology of vasospasm is not clear, but is thought to occur secondary to both general and local factors. General factors include low core temperatures, hypotension, and sympathetic response to pain, while local factors include trauma to the vessel, tight adventitia, myogenic response to local hemorrhage, desiccation of the tissues, and vascular disease. Surgical dissection may induce sympathetic nerve endings to release vasoactive compounds, and impair release of vasodilators,²⁵² compounding the vasospasm and thrombosis. Veins appear to be less susceptible to vasospasm than arteries but, once established, harder to resolve²⁵³ and more detrimental.

If the vessel is left untouched for a few minutes, it may vasodilate to its natural diameter. However, a variety of antispasmodic agents or mechanical dilation can be used to aid relief of the vasospasm.

Most of the antispasmodic agents available are locally applied to avoid systemic complications. The most commonly used agents are papaverine, lidocaine, and calcium channel blockers such as nifedipine, verapamil, and nicardipine. Papaverine (30 mg/mL) is an opium alkaloid that functions as a phosphodiesterase inhibitor and has a direct action on smooth muscle through the release of cyclic adenosine monophosphate. Lidocaine is a local anesthetic agent that has a biphasic response with low and high concentrations potentiating contraction and dilatation, respectively.²⁵⁴ Its vasodilatory mechanism remains unclear but is thought to be related to sodium–calcium exchange pump. Some studies suggest that its concentration should be increased up to 20% or be combined with papaverine.²⁵⁵ The benefit of lidocaine continues after the drug is washed out with heparinized saline solution and, as it is not significantly absorbed from the wound, systemic effects are unlikely.²⁵⁶ In practice, however, common concentrations of lidocaine used vary between 2 and 4%.²⁵⁷ Calcium channel blockers work by blocking voltage-gated calcium channels in vascular smooth muscle. This blocks the calcium influx required for muscle contraction and may even be more effective than papaverine.²⁵⁸ Sympathetic blockade using brachial plexus blocks has also been reported to be effective.^{259–261}

Mechanical treatments of vasospasm include gently dilating healthy vessel ends with a specially designed blunt-ended vessel dilator forceps or with microneedle holders. Metallic standard-sized dilators or intraluminal irrigation through the passage of a fine intracath may also be used. This should be done with caution, especially in arteriosclerotic vessels, as catheters can strip endothelium and expose the thrombogenic subendothelium.²⁶² Surgical stripping of adventitia is an effective method of relieving vasospasm because of a sympathectomy effect and mechanical thinning of the vessel walls allows them to dilate more freely.²⁶³ If the spasm is intractable, the vessel should be aggressively resected until normal vessel is reached. Occasionally this may require an additional vein graft or turning to another recipient vessel for anastomosis.

Stable and thorough anesthesia is an important requirement: hypovolemia, pain, and low core temperature (<36°C) can all result in vasospasm. The patient's temperature should be constantly monitored and adequate hydration maintained, and the wound should not be allowed to dry out.

Thrombogenesis

Many free-flap complications relate to pedicle thrombosis (4–80% within the first 48 hours) caused by changes in the intraluminal blood flow, endothelial damage, and the state of coagulability. Changes in flow can be due to external mechanical compression from bandages, closure of the wound under tension, the weight of the flap, tension, twisting, kinking, or vasospasm of the vascular pedicle after the anastomosis is completed. Intraluminal turbulence may be caused by irregularities in the intima from technical error, suture material, and the result of size mismatch.

Hypercoagulability may be systemic or local. Hypercoagulable states such as pregnancy, active cancer, and recent trauma should be identified preoperatively as far as possible and warrant thromboprophylaxis. Hypercoagulation disorders like activated protein C,²⁶⁴ hyperfibrinogenemia,²⁶⁵ antiphospholipid syndrome,²⁶⁶ and reactive thrombocytosis²⁶⁷

should be treated preoperatively, although routine screening for these is not cost-effective. Thromboplastins are soluble in water and present in abundance in the surgical wound. When blood is contaminated by this, clotting will occur and periodic irrigation with heparinized saline will minimize this risk. Even a smooth and streamlined microvascular anastomosis will produce some thrombus, and when blood flow is restored, the thrombus continues to grow for 5 minutes, starts to disintegrate by 10 minutes, and disappears nearly completely by the end of an hour. If the anastomosis is irregular, the thrombus will grow rapidly and occlude the vessel. Endothelial cells are critical in local blood flow control and produce vasoconstrictors such as endothelin-1^{268,269} and vasodilator substances, nitric oxide and prostacyclin. Damaged endothelium produces a highly thrombogenic state, resulting in platelet aggregation and the initiation of a complex clotting cascade, and surgical precision is vital to minimize vessel damage.²⁷⁰

The risk of thrombosis is greatest within the first 48 hours and decreases to 10% after 72 hours.²²⁹ Arterial and venous thrombi present at different times and form through different mechanisms. The majority of arterial thromboses occur during the first 24 hours and are related to platelet aggregation at the anastomotic site.²⁷¹ Venous thrombosis is more often responsible for flap compromise, presents later, and is related to the formation of a fibrin clot. The goals of anticoagulant prophylaxis are therefore to interfere with platelet function and aggregation, counter the effects of thrombin on platelets and fibrinogen, and reduce blood viscosity or increase blood flow.²⁷² While the use of anticoagulants to lower the incidence of anastomotic thrombosis is widely practiced, literature regarding the efficacy of one treatment over another is sparse and largely based on the individual surgeon's preference and preconceptions. Protocols differ not only in the agents used, but also the dose, combination, timing, and duration. Heparin, dextran, and aspirin are the most commonly used prophylactic antithrombotics today.

Heparin reduces platelet aggregation, activates antithrombin III (thereby directly deactivating clotting factors II, IX, X, XI and, indirectly, factors V and VIII), lowers blood viscosity, and has direct vasodilatory properties.²⁷³ This polyglycosaminoglycan was the first anticoagulant described and has been in clinical use for over 50 years to prevent both arterial and venous thromboses, even at subtherapeutic levels²⁷⁴ and independent of rate of blood flow. As a washout solution, it may have a protective effect against ischemia/reperfusion injury through a direct effect on microvascular endothelium.²⁷⁵ Intravascular heparin improves flap salvage rates²⁷⁶ and clinically reduces the rate of thrombotic events.¹¹¹ Its use, however, may be more important in patients with atherosclerotic or injured vessels, when vein grafts have been used and with thrombosis of an anastomosis, than in patients with healthy vessels and straightforward anastomoses.²⁷⁷ The use of intravascular unfractionated heparin may increase the risk of hematoma formation,^{278,279} but both Chien *et al.*²⁸⁰ and Kroll *et al.*²⁸¹ have found that flap survival was equivalent to that with other regimens without increased incidence of hematoma. Low-molecular-weight heparins, which inhibit clotting factor Xa with less of an effect on thrombin inactivation, may be just as effective in improving patency without the risk of hematoma formation.²⁸² Unfractionated heparin is used universally to irrigate vessels during microvascular surgery and has been shown experimentally to improve patency when

administered at high concentrations^{44,283,284} while minimizing the systemic complications. Heparin binds to the endothelium and has a half-life of 5 hours²⁸⁵ and should be applied as soon as the vessels are divided. Clinically, however, Khouri showed no increase in patency regardless of concentration¹¹¹ and Yan suggested that high-pressure local irrigation might even cause intimal and endothelial damage.²⁸⁶ Nevertheless, together with another important side effect of heparin-induced thrombocytopenia, systemically administered heparin should be used judiciously.

Dextran is a polysaccharide synthesized from sucrose and produced synthetically as a 40- or 70-kDa molecular weight polymer. Its antithrombotic effect is mediated through increasing the electronegativity of erythrocytes, platelets, and endothelium and therefore platelet aggregation, decreasing factor VIII-Ag and thereby platelet function and fibrin structure, and, finally, as a volume expander that reduces blood viscosity. Dextran-40, the more popular dextran for anticoagulation in microsurgery,^{111,281,287} is excreted more effectively by the kidneys and has a shorter action than dextran-70. No randomized controlled studies have shown a cause-and-effect relationship between the use of dextran and flap loss or prevention of thrombosis. In particular, it has not been shown to be more effective than other anticoagulants and its benefits of improved vessel patency are not seen beyond a week.^{288,289} Although it has relatively few side effects, these can be serious and include anaphylaxis, volume overload, pulmonary or cerebral edema, platelet dysfunction, and even acute renal failure.^{290,291} A comparison of dextran and aspirin-related complications in head and neck patients with free-flap reconstructions showed that both were equally effective in preventing flap failure, but dextran was associated with a 3.9- and 7.2-fold increased relative risk of systemic complications after 48 and 120 hours of dextran infusion, respectively.²⁹²

Aspirin is an antiplatelet agent that inhibits cyclooxygenase and reduces the breakdown of arachidonic acid to thromboxane, a potent vasoconstrictor and platelet aggregator, and prostacyclin, a vasodilator that inhibits platelet aggregation. Low-dose aspirin (75 mg/day) has been shown to inhibit thromboxane selectively at the site of the anastomosis²⁹³ while preserving prostacyclin production of the endothelium. Experimentally, it has been shown to improve anastomotic patency and capillary perfusion and may be related to the timing of administration.^{294,295} It is, however, less effective than heparin^{295,296} and, despite the lack of clinical evidence for its effect on free-flap patency, it is still used widely. The adverse effects of aspirin such as gastric hemorrhage, renal failure, and prolonged bleeding are a direct result of the mechanisms that make its use attractive in microsurgery and have been minimized with the use of low-dose aspirin. The newer cyclooxygenase II inhibitors are also associated with fewer renal and gastric side-effects but do not prevent platelet aggregation and are therefore not used in microsurgery.²⁹⁷

Prostaglandin E1 is known for its application in peripheral arterial occlusive disease. It has long-standing anti-ischemic and tissue-protecting effects against ischemia-reperfusion injury. It is capable of relieving microvascular spasm and increases deformability of red cells; in addition to the positive impact on blood flow, viscosity, and platelet aggregation.²⁹⁸ Thrombotic diathesis can be reduced by using a low dose in arterioles, or a high dose in venules.²⁹⁹ It is commonly used in replantation, toe-to-hand microsurgical transplantation, and

other free flap transfer. Despite the promising results reported earlier, a large study analyzing whether prostaglandin-E1 (PGE1) and dextran-40 can improve the outcomes compared to no-antithrombotic therapy in head and neck reconstruction revealed no significant difference among PGE1, dextran-40, and control group in flap survival.³⁰⁰ Other antithrombotic agents tested in animal models to determine their efficacy in augmenting flap survival include pentoxifylline,³⁰¹ hirudin,²⁸⁴ nonsteroidal anti-inflammatories,^{302,303} other antiplatelets such as dipyridamole and ticlopidine.³⁰⁴

Thrombolytics such as streptokinase, urokinase, and tissue plasminogen activator have been advocated for flaps not responding to standard salvage techniques²⁴⁸ and may be effective in reversing microvascular thrombosis,^{249,250} but clinical evidence is sparse and anecdotal.³⁰⁵⁻³⁰⁸ A retrospective multi-institutional study even reported no significant improvement in patency with the use of thrombolytic therapy in free-flap salvage.³⁰⁹ Streptokinase enhances the conversion of plasminogen to plasmin with subsequent fibrinolysis, whilst urokinase and tissue-type plasminogen activator, which activate plasminogen directly, are less antigenic and have fewer systemic effects. There is a significant risk of bleeding following systemic exposure to thrombolytics but this can be minimized by local intra-arterial administration of the thrombolytic and drainage of the venous effluent.³¹⁰

When surgical and pharmacological salvage fails, medicinal leeches (*Hirudo medicinalis*) have been used effectively to treat venous congested flaps.³¹¹ When applied to the flap, they bite into it, injecting a local anesthetic, vasodilator, and anti-coagulant, hirudin, which is present in their saliva. Leeches increase perfusion within congested flaps by feeding on the blood. They then fall away when full, but the bleeding continues for up to 10 hours with the combination of vasodilator and anticoagulant.³¹² New leeches can be applied when the bleeding slows or the flap appears congested again. Therapy is continued until the flap re-establishes an effective venous drainage through new vessel ingrowth around the flap margins. As there can be significant blood loss with leech therapy, this is usually limited to small- to medium-sized flaps and the patient's hemoglobin should be monitored daily. Prophylactic antibiotics should also be given against *Aeromonas hydrophila* from the leeches' digestive tract.

Ischemic tolerance, ischaemia-reperfusion injury, and no-reflow phenomenon

Prolonged periods of warm ischemia (the time between interruption and re-establishment of the circulation) concern microsurgeons as they predispose to tissue necrosis and flap failure. Primary ischemia occurs when the anastomosis is being performed and can be kept to a minimum by donor site and vessel preparation before flap pedicle division and an accurate anastomosis, whilst secondary ischemia occurs later as a result of pedicle obstruction.

The tolerance to ischemia varies from tissue to tissue depending on their metabolic requirements, with skin, nerve, bone, muscle, and then intestine being decreasingly tolerant. Within a composite flap, the overall tolerance is equal to that of the least tolerant component. A study of 700 free flaps failed to show a statistical difference in ischemic times between successful and failed flaps and concluded that ischemic time was irrelevant to flap survival provided ischemia was not

prolonged beyond 3 hours or to the point of "no-reflow phenomenon".

While the goal of microsurgical anastomosis is to restore flow and reperfuse the flap, after a prolonged period of ischemia, this reperfusion may compound insult to the flap through local and systemic inflammatory responses. This is known as ischemia-reperfusion injury and is thought to be a result of the buildup of oxygen radicals during the ischemic period. These cause tissue injury, specifically of cellular membranes through their powerful oxidizing and reducing potentials. They also stimulate an intense inflammatory reaction by recruiting inflammatory cells such as leukocytes, neutrophils, and platelets, and other inflammatory mediators and cytokines,³¹³ while suppressing protective molecules such as nitric oxide synthase, prostacyclin, and thrombomodulin. In clinical free flaps, a similar pathophysiology was also found. From a histological and molecular point of view, significant up-regulation of inflammatory parameters, in particular interleukin-1 β and tumor necrosis factor α , infiltration of inflammatory cells, and angiogenesis were documented. Increased complement component 3 deposition and apoptosis of cells were accompanied by interstitial edema as indication for a pronounced postischemic inflammatory reaction within the muscle tissue after free tissue transfer.³¹⁴ In cutaneous flaps, a significant decrease in total hydrophilic antioxidant capacity (TEAC) was seen.³¹⁵ These findings provided insights into some effective treatment modalities to minimize the damage induced by ischemia-reperfusion injury as discussed below.

Severe ischemia-reperfusion injury results in irreversible vasoconstriction, and the resulting inability to reperfuse the flap despite patent anastomoses is known as the "no-reflow phenomenon".³¹⁶ This is a result of ischemia-induced endothelial injury, which leads to cellular swelling, interstitial swelling, exposure of subendothelial collagen, platelet-leukocyte aggregation, reduction in blood flow and, if not rectified, thrombosis and flap failure.

Experimental studies have shown a protective function of intravascular administration of heparin,^{275,317} vasodilators, prostaglandin E₁, nitrendipine and prostacyclin, thrombolytics, urokinase and streptokinase, nonsteroidal anti-inflammatory drugs, and free radical scavengers deferoxamine and superoxide dismutase.^{318,319} Inhibiting the action of selectins, integrins, and intercellular adhesion molecules with monoclonal antibodies to prevent inflammatory cell adhesion may also prevent ischemia-reperfusion injury, but these have not translated clinically.^{320,321}

Clinically, few pharmacological agents have been used and proved promising. One treatment modality aimed at increasing microcirculation within the transverse rectus abdominis muscle flap by continuous IV administration of arginine showed significant improvement in zone IV perfusion.³²² While the other aimed at reducing the inflammatory response and the interstitial edema by applying negative wound therapy on top of the skin grafted muscle flaps with remarkable reduction in interleukin-1 β and tumor necrosis factor α in biopsies.³²³ The last targeted the endothelial dysfunction using statins drawing on their pleiotropic effects,³²⁴ however, a larger study failed to show clear advantages of the statins or other cardiovascular medications in ischemia-reperfusion injury.³²⁵ So, the benefit of statins remain theoretical, and their usage is limited to patients with cardiovascular diseases.

Donor site complications – dependent again on flap choice

Every flap harvested leaves a donor site of varying morbidity; therefore, the benefits of the reconstruction must outweigh its sequelae. The incidence of donor site complications varies between 5.5% and 31%, with early donor problems associated with wound healing (hematoma, seroma, and wound dehiscence).^{326,327} These are more likely in obese patients, diabetics, and smokers. Hematomas may occur with any flap harvest and meticulous hemostasis with a normotensive (for the patient) blood pressure must be performed. Seromas occur when extensive dissections leave large dead spaces, for example, with a latissimus dorsi or deep inferior epigastric perforator harvest, and wound dehiscence occurs with tight closure, which can be avoided with good preoperative planning.

Long-term problems are usually that of poor cosmesis, reduced function, and chronic pain. If the donor site has to be grafted, this causes a significant cosmetic disadvantage and patient dissatisfaction.^{327–330} Suprafascial dissection reduces the size of the donor defect, allows preservation of the superficial nerves, prevents tenting of tendons, and improves skin graft take. This allows a full-thickness skin graft with superior cosmesis to be applied with confidence and reduces potential tendon exposure from delayed healing.^{330–332} Muscle flaps may cause weakness and functional impairment; for example, serratus anterior muscle elevation may cause scapular winging and the TRAM flap is associated with hernia formation.^{333,334} Harvesting vascularized bone may result in impaired function of a fracture-susceptible donor site, requiring troublesome splinting for a prolonged period,^{326,335} and even affecting gait. Cutaneous nerves may be sacrificed, leaving painful neuromas or unacceptable numbness.^{335–337} Temporary or permanent palsies may result from injured motor nerves and compartment syndrome from overzealous closures.³³⁸

Management of failed flaps

Flap failure has profound implications on both patient and surgeon and represents one of the most challenging aspects of reconstructive microsurgery. Despite the increased experience and refinements in microsurgical techniques and perioperative management, a small number of flaps still fail. With the low incidence of flap failure, there are few articles in the literature that address the management of flap failure and no guidelines regarding the best approach to this problem exist.

Many questions are raised immediately when a flap fails. Why did it happen? What defect requires reconstruction? How and when should the defect be reconstructed? These questions invariably form the basis of a systematic approach to the problem at hand and should be considered when managing a failed flap. Analyzing 54 failed flaps, Oliva *et al.*²⁵ recommend that three issues must be considered when the initial flap is declared nonviable – the reasons for failure, the indications for the free-flap reconstruction, and the current status of the resultant wound.

It is important to identify the reasons for the failure as subsequent attempts at reconstruction might be plagued with the same issues and be doomed to fail. If the cause is reversible or preventable, then this bodes well for a repeat

attempt with another free flap. Examples include technical errors, suboptimal postoperative management, and delay in diagnosis and salvage. Irreversible patient factors like systemic vascular disease, radiation injury, and lack of healthy recipient vessels do not preclude a further attempt but the decision to proceed with a second microsurgical reconstruction should be weighed carefully against the risks. If the risks outweigh the benefits, a nonmicrosurgical procedure may be the sensible option, although this may be just as complicated.

The need for further reconstruction is then evaluated. Factors to be considered include the extent of the failure,³³⁹ exposure of vital structures, and the effect of an open wound on subsequent therapy. An important question to address is whether the initial goal of a sophisticated reconstruction should be pursued or if a downgraded reconstruction is an acceptable compromise between achieving wound closure and the aesthetic and functional goals. Partial loss of a flap secondary to necrosis may be amenable to conservative treatment with conventional dressings, vacuum-assisted closure, or skin graft. Complete failures, such as those due to arterial insufficiency, are more catastrophic and require more aggressive treatment while venous failures deserve a more expectant management with the use of medicinal leeches or by allowing the flap to bleed out slowly to allow partial salvage. This may support a skin graft after tangential debridement.³³⁹ If the flap loss results in exposure of vital structures such as the great vessels of the neck, skull base, metal plates or bare bone, the situation may be life-threatening and mandates prompt coverage with another flap.³⁴⁰ For breast reconstruction, it is reasonable to consider primary or secondary closure if the patient can accept the cosmetic implications. In extremity reconstruction, where the threat is isolated to the extremity involved, a more expectant approach can be taken, provided metal plates or vital structures are not exposed. Less aggressive management may, however, result in higher rates of limb amputation.³⁴¹ In oncological reconstruction, the primary goal is uncomplicated wound healing in order that adjuvant therapy can proceed. In these circumstances a second flap will expedite wound healing and should be considered early. A pedicled muscle or cutaneous flap might be a reasonable alternative to a free flap, if the factors involved are irreversible or the risk of a second free flap outweighs the benefits.

Once the decision has been made to proceed, the course of action needs detailed planning. Factors to be considered include the timing of the repeat surgery, the type of reconstruction required for the resulting defect, and if there is a need for a second free flap. If a second free flap is needed, then what donor sites are available and what recipient vessels can be reliably dissected and safely used? Importantly, are the goals of reconstruction the same as they were initially?

The timing of the surgery is dependent on several factors. If the patient is unstable, then reoperation is ideally delayed. Infection-free, the flap may act as a temporizing biological dressing until the patient is fit for further surgery. The recipient site and exposure of vital structures may dictate the urgency of the surgery. If the patient is fit enough, the same second free flap should be performed at the time of adequate debridement.²⁵ In our experience of 101 failed free flaps, 34% received a second free flap³⁴⁰ and we feel a second

free flap should be attempted in any case in which failure may lead to loss of the injured limb, leave exposed major neck vessels, or cause delay in adjuvant chemo- or radiotherapy. Restoration of function should also be attempted in a previous functional muscle transfer. The success rate of second free flaps is higher in the head and neck region (94.1%) compared to that in the extremity (82.2–87.5%).^{340,342} A downgrade of reconstruction should only be considered if the patient is not in optimal condition or in the presence of overwhelming infection as this often results in poorer cosmetic and functional outcomes.

The second free flap needs to be chosen and designed carefully. It should have good vascularity and a longer pedicle as debridement may leave a larger defect, and the new recipient vessels are likely to be further from the defect. Where possible, do not reuse the previous recipient vessels as they are likely to be inflamed and friable. Interpositional vein grafts may be required but have been associated with a higher incidence of flap failure and vascular complications.^{343,344} If the same flap is available on the contralateral side, this is our flap of choice and was most commonly used.³⁴⁰ However, as it is generally accepted that a flap with an osseous component poses additional difficulties during flap elevation and inset and has been associated with a higher failure rate,¹³³ a safer option should be considered. Other indications for choosing a different type of flap (for example, choosing a myocutaneous, fasciocutaneous, or even pedicled flap with reconstruction plate over an osteocutaneous flap) include the absence (abdominal flaps) or unavailability of the contralateral side (already used or in the zone of injury) or a downgrading of the reconstructive goals due to patient fitness, altered prognosis, or the need to ensure survival.

The future of microsurgery

Has microsurgery reached a status quo yet? Or, will innovations and breakthroughs continue to endure? The authors believe that there are no definite answers to these questions; however, there could be a good chance to make a better use of microsurgery in future by proper planning and smart investment.

The following potential directions reflect some of the authors' ideas on microsurgery in the digital era.

Digital technology is always evolving and will most likely continue to evolve. Intertwining technology and microsurgery together will be a "game changer" in our practice.

Smart phone apps may revolutionize free flap monitoring³⁴⁵ and probably the whole perioperative workup by providing surgeon-friendly, fast, and, efficient tools for communication, assessment, and advice.

Google Glass or any similar products with live streaming of the surgical procedures utilizing the 4G or high-speed internet may help in telesupervision of trainees for a safer hands-on training experience.

Other technological advancements in the fields of high definition magnification and imaging can improve our understanding of the fine circulation of skin, muscles, bones, etc., resulting in custom-designed free tissue transfer; an even more refined form of supermicrosurgery.

Robots are already in use, but a specialized microsurgery robot is still lacking, which could be a product of the future; however, the wide application of robotic surgery may not witness significant change not only because of its cost but also due to limited indications.

How about the technical part itself, such as the microanastomosis, the dissection techniques, inset, etc? While the standard techniques described in the chapter will remain in use heavily, the trend towards sutureless and minimal-access surgery (in other words, a traumaless approach) will most likely continue to grow.

As for flaps and donor sites, we believe that every microsurgeon or center will have their own workhorse flaps that they rely on to achieve the reconstruction goals; however, free flaps from the lower extremity will most likely prevail over other flaps for the advantages of two-team approach and diversity of options.

Many authors have already mentioned that vascularized composite tissue allotransplantation (VCA) is the frontier to conquer, and it could be the future of microsurgery! We do not very much share that vision. This is because microsurgery is a technique utilized in the field of VCA not the opposite. Second, the main obstacle to broader application of VCA is immunosuppression not microsurgery. Although hand transplantation is not "another replantation", it relies on the same techniques used in replantation and toe-to-hand surgery. And face transplantation has its roots in facelift techniques and facial trauma and orthognathic surgery. So, the techniques are already established, and only a breakthrough in immunosuppression will lead to a revolution in VCA. Hand transplantation recorded number one in VCA may lose ground with the development of smart prosthesis. However, face transplantation may witness a flourishing future since results are encouraging and no alternative option is available, not to mention the increase in war casualties among civilians nowadays.

Finally, our words to history; microsurgery will not decline: the growing interest in learning microsurgery and the lack of comparable techniques will ensure this. Furthermore, microsurgery may become an independent specialty instead of a set of skills used by different specialties, but mainly plastic surgery. And technological refinements and breakthroughs will definitely shape the theme of future microsurgery.



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Principles and applications of tissue expansion

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SYNOPSIS

- Tissue expansion is a time-tested and simple technique to generate tissue to reconstruct defects.
- The technique stretches skin and soft tissue that have the same color and texture as the adjoining skin where expanded tissue is needed.
- In the breast, expansion is particularly useful in stretching existing anatomy to accommodate a permanent prosthesis.
- Tissue expansion principles may be combined with other reconstructive techniques to provide a safe and individualized reconstructive plan for complex bodily defects.

Introduction

The plastic nature of the human integument can be witnessed whenever the skin must allow for growth underneath it. The surgeon can take advantage of this plasticity when either medical need or aesthetic surgery would benefit from the creation of new autogenous skin. Just as development of a fetal brain will cause the overlying skull to grow, growth of the skeleton causes all normal skin and soft tissues that envelope the bone to respond and expand. Similarly, the growth of other structures inside the body will cause skin and subcutaneous tissues to expand as demonstrated by the serial growth of the abdomen with successive pregnancies. Whether the growth is caused by benign or malignant tumors under histologically normal skin or is experienced in the gravid abdomen, there is a clear response to non-genetic stimuli allowing necessary growth to accommodate underlying structures.

Since its introduction, the benefits of tissue expansion have produced a significant evolution of therapeutic techniques since donor tissue may be generated *in situ* and used for reconstruction without compromise of innervation, vascularity, or external physical appearance. One of the critical benefits of tissue expansion is the fact that there are various methods for expansion of skin, bone, and other tissues. Placement of a

prosthesis under soft tissues allows the surgeon to gradually add saline and expand subcutaneous and cutaneous tissues. External hardware is used to gradually expand fractured bone through the application of distraction forces. These techniques have been applied to the craniofacial skeleton as well as to most of the long bones of the body.^{1,2} Similarly, negative pressure wound therapy (NPWT) uses the principle of applying mechanical force to cells surrounding a wound to stimulate the induction of new tissue that will subsequently aid in closure of that wound.³



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Basic science

Cellular and molecular basis for tissue expansion

The application of mechanical stress to living tissues and cells affects various cell structures and signaling pathways that are highly integrated (Fig. 25.1).¹⁵ These closely integrated cascades are theorized to explain the generation of new tissue through mechanical stimulation.¹⁶ Several *in vitro* stretching systems have been used to better understand the molecular events that occur.¹⁷ Mechanical deformation forces involve several cellular mechanisms including the cytoskeleton system, extracellular matrix, enzyme activation, secondary messengers, and ion channels.

The cytoskeleton plays a critical role in mediating the transformation of extracellular mechanical force to intracellular events. A system of microfilaments within the cytoplasm not only maintains intracellular tension and cell structure but also transduces signals to adjacent cells and initiates transduction cascades within the cell (Fig. 25.2).¹⁶ Protein kinase C plays a pivotal role in signal transduction. Mechanical strain

Historical perspective

In 1905, Codvilla applied the principles of using an external, distractive force to encourage tissue expansion in bone.⁴ Bone tissue regeneration was later documented in 1970 by Ilizarov and others, who provided roentgenographic and morphologic data from experimental distraction epiphysiolysis.² Shortly thereafter, Matev reported the expansion of bony tissue after amputation of the thumb at the metacarpophalangeal joint.⁵

In the meantime, physicians began to recognize the induction of new soft-tissue growth adjacent to the bony structures undergoing gradual lengthening. In 1957, Neumann implanted a subcutaneous balloon to induce soft-tissue growth purposefully for the reconstruction of an external ear deformity.⁶ Unfortunately, his report was considered anecdotal so progress in surgical soft-tissue expansion was delayed until the

1982 reports of using implanted silicone balloons to expand overlying soft tissue were published.

Radovan⁷ and Austad⁸ and Rose⁹ simultaneously developed the concept of implanting silicone balloons as expanders. Austad's prosthesis was a self-inflating device that used osmotic gradients driven by salt placed within the expander. His largely experimental work was critical to elucidating the physiology of tissue expansion.

Radovan's device contained a self-sealing valve through which saline was periodically injected to increase the size of the expander. His work was initially greeted with skepticism. Despite this, Grabb's enthusiastic acceptance of Radovan's technique stimulated its rapid and wide application to create new horizons in reconstructive surgery.¹⁰⁻¹⁴ Large studies subsequently confirmed the safety and efficacy of this technique.

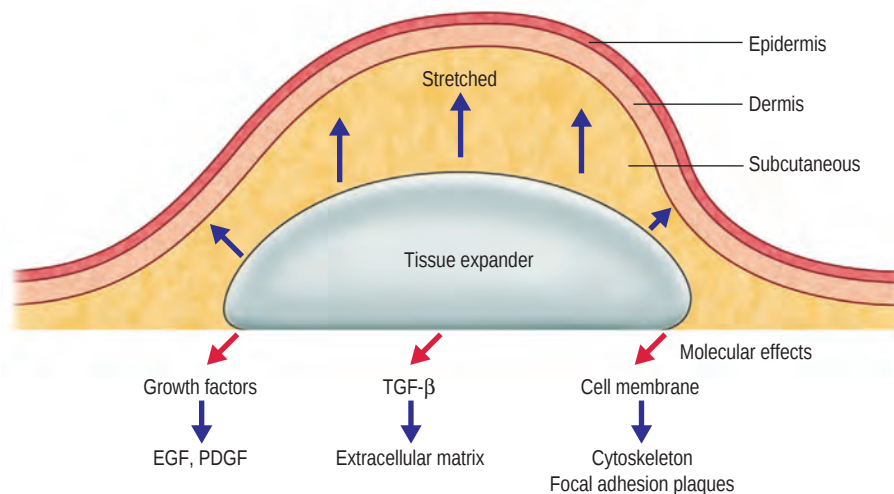


Fig. 25.1 Effects of tissue expansion on surrounding tissue. Strain-induced responses are mediated by growth factors such as platelet-derived growth factor (PDGF) that are known to stimulate cutaneous cell proliferation. Other growth factors such as transforming growth factor- β (TGF- β) may stimulate extracellular matrix production. Membrane-bound molecules including protein kinase play a key role in regulating intracellular signaling cascades. EGF, epidermal growth factor. (Adapted from Takei T, Mills I, Arai K, et al. *Molecular bases for tissue expansion: clinical implications for surgeon*. *Plast Reconstr Surg*. 1998;102:247–258.)

on cell walls activates inositol phosphatase, phospholipase A₂, phospholipase D, and other messengers. Activation of these components leads to activation of protein kinase C, which suggests that intracellular signals can be transmitted to the nucleus. Protein kinase C activation has been noted in human cells subjected to strain *in vitro*.¹⁶

The mechanical effects of negative pressure wound therapy (NPWT) on wounded tissues and their subsequent cellular and molecular effects are actively being studied. At a cellular level, NPWT alters wound bed gene

expression with resultant changes in cytokine/chemokine/growth factor expression and matrix metalloproteinase expression. In human and animal models, increases in anti-inflammatory cytokines (IL-10) and pro-angiogenic growth factors (VEGF, FGF, PDGF) have been demonstrated with the use of NPWT. The above, in conjunction with reduction in MMP expression, indicates that NPWT may promote healing by modulation of cytokines to an anti-inflammatory profile and alteration in mechanoreceptor and chemoreceptor mediated signaling to culminate in angiogenesis and

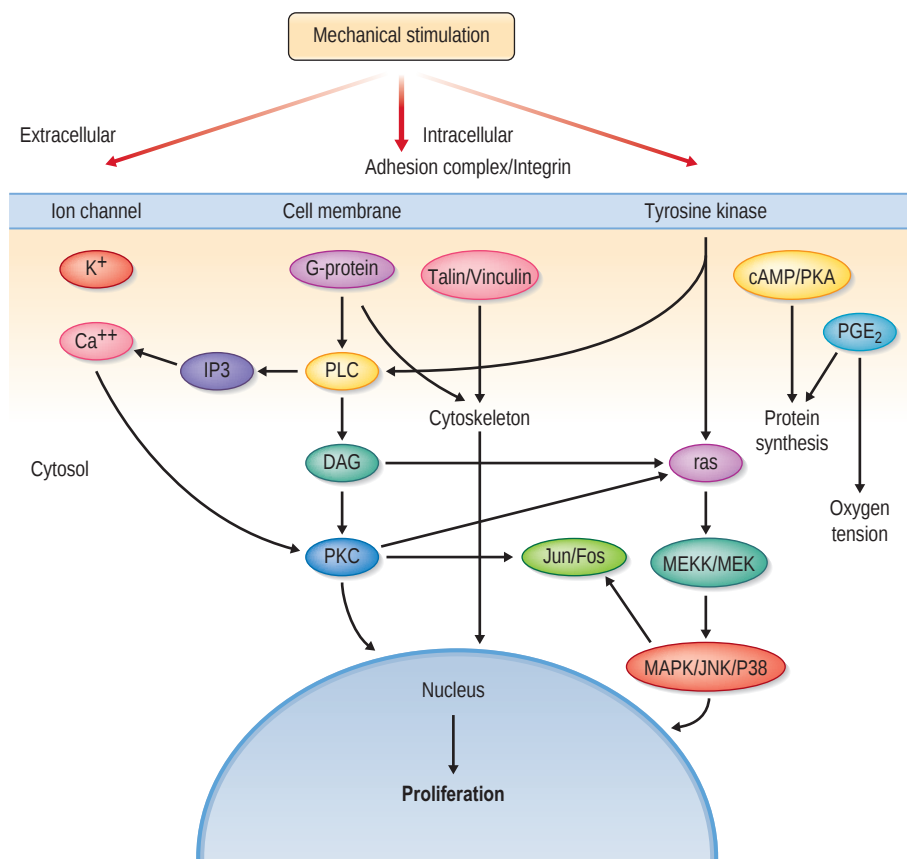


Fig. 25.2 Schematic of possible signal transduction pathways induced by mechanical strain. Transduction pathways are activated by numerous strain-induced signals transmitted through various membrane receptor or membrane ion channels. Terminal enzymes that are activated by these intracellular cascades transduce these signals into the nucleus. cAMP, cyclic adenosine monophosphate; DAG, diacylglycerol; IP₃, inositol 1,4,5-triphosphate; JNK, c-Jun amino-terminal kinase; MEKK/MEK/MAPK, mitogen-activated kinases; PGE₂, prostaglandin E₂; PKA, protein kinase A; PKC, protein kinase C; PLC, phospholipase C.

extracellular matrix remodeling for the deposition of granulation tissue.¹⁸

Biology of tissue expansion

Extensive information is available regarding the biology of tissue expansion. After the completion of animal experiments,^{9,19} studies on human tissue examined the process of tissue expansion that occurs both during the period of expansion and postoperatively.²⁰ Studies of the effects of tissue expansion on nerve, muscle, and bone have also been published.

Skin

Statistical analysis of multiple sites over the implant and its periphery has revealed a significant increase in epidermal thickness during the process of expansion and this thickening occurs soon after expander placement. This is also seen in sham controls and may represent, in part, postoperative edema. Within 4–6 weeks, epidermal thickness generally returns to initial levels, but some increase in thickness persists for many months.

The increased area of skin over the expander includes not only normal skin recruited from adjacent areas but also new skin generated by increased cellular mitosis.²¹ Hair follicles are not reproduced in humans, so individual follicles are distracted during expansion. Distraction between follicles is less noticeable in blondes than in dark-haired individuals. Melanocytic activity is increased during expansion but returns to normal levels within several months after completion of the reconstruction. Although hair follicles and accessory skin structures are compressed by tissue expansion devices, they show no evidence of degeneration.

During expansion, the dermis decreases rapidly in thickness over the entire implant. Thinning is most pronounced in the first several weeks after implant placement and persists for the entire period of expansion. Dermal thinning persists at least 36 weeks after expansion is completed.²²

Capsule

A dense fibrous capsule that becomes less cellular over time develops around the implant. Progressive collagen deposition occurs over 3 months with the development of well-organized collagen bundles. Molecular studies have demonstrated up-regulation of the wingless (Wnt) signaling pathway in the pathogenesis of inflammation and capsule fibroproliferation which may contribute to capsular contracture seen after radiation therapy in breast cancer patients. Such increases have not been demonstrated in non-irradiated tissue. This is further supported by the growing body of evidence demonstrating decreases in inflammatory markers and limited capsule formation associated with the use of acellular dermal matrices (ADMs).²³ Although no evidence of dysplastic changes or loss of normal cell maturation has been observed, dystrophic capsular calcification may occur with repeated trauma to the prosthesis or with hematoma resolution. After prosthetic removal, the capsule resolves and little clinical or histologic evidence of it remains over time. Histological examination of capsular tissue demonstrates an extensive vascular plexus within collagen such that capsule itself can be harvested as a local flap because of this induced vascularity.

Muscle

Muscle atrophies significantly during the process of expansion, whether the prosthesis is placed above or below a specific muscle. The effects on human muscle after expansion during breast reconstruction have shown occasional histologic ulceration. Focal muscle fiber degeneration with glycogen deposition and mild interstitial fibrosis has been identified. In addition, some muscle fibers show disorganization of the myofibrils in the sarcomeres.²⁴ Animal studies on the morphologic changes in skeletal muscle suggest that the expansion of skeletal muscle is not a stretching process but is rather a growth process of the muscle cell accompanied by an increase in the number of sarcomeres per fiber. Expanded skeletal muscle returns to normal muscle architecture, vasculature, and function after the prosthesis is removed.²⁵ Moreover, muscle mass returns to normal levels after removal of the device in humans.

Bone

The effect of expansion on underlying cranial bone has been studied in animal models. Decreases in both cranial bone thickness and volume are evident beneath the expander where bone resorption occurs. In contrast, there is an increase in bony thickness predominantly at the expander periphery where a periosteal inflammatory reaction is seen. Bone density is unaffected.

Expansion over the cranium in children under one year of age should be done judiciously. Depression of cranial bone during expansion may occur before one year of age but usually corrects itself once the expander is removed. In the face of expansion, cranial bone appears to be measurably more affected in thickness when compared to that of long bone. Long bone remodeling begins within 5 days after removal of the expander and the long bone is completely normal within 2 months. Remodeling in cranial bone is complete in 2–3 months.

Vascularity of expanded tissue

The robust vascularity of expanded tissue was clinically evident long before laboratory work measured it (Fig. 25.3). It has been clinically and histologically demonstrated that a large number of new vessels are formed adjacent to the capsule.²⁶

The content of collagen fibers in existing vessels initially decreases after expansion while elastic fibers in existing blood vessels initially increase in response to mechanical stress. Angiogenesis occurs in response to induced ischemia of the expanded tissues. The number of cells expressing vascular endothelial growth factor (VEGF) is significantly higher in expanded tissue than in non-expanded, similar tissue.²⁷ Expanded fascial flaps show a measurable increase in vascularity between the fascia and subcutaneous tissue. Increased perfusion to the distal and peripheral areas of the flap also increases the robustness of the flap and the possibility of harvesting a larger flap.²⁶ Similar studies on prefabricated, expanded, pedicled flaps have shown increased vascularity within the pedicle, as well as in the adjacent random areas.²⁸

The increase in vascularity affords the expanded tissue important functional benefits. Animal studies have shown that flaps elevated in expanded tissue have significantly

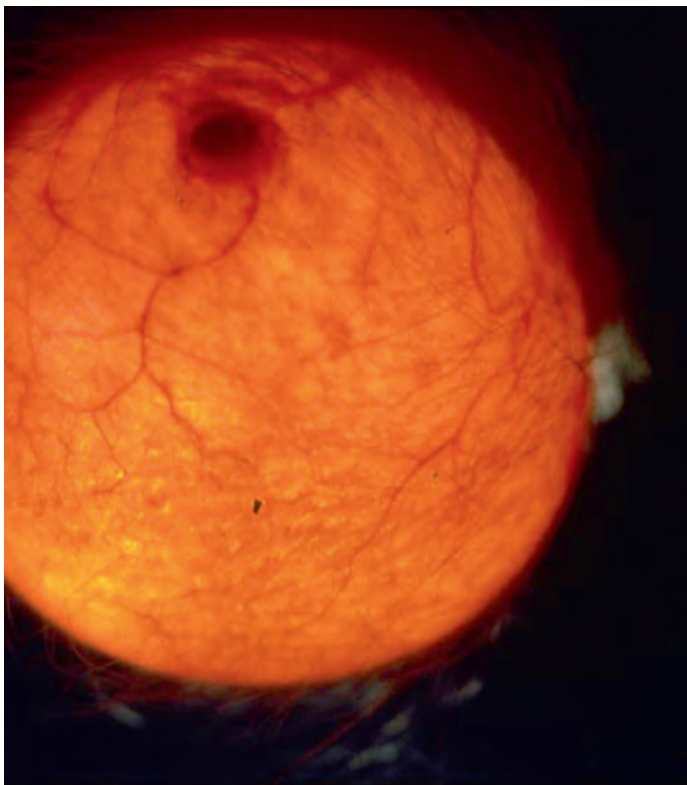


Fig. 25.3 Transillumination of expanded human skin demonstrating an intense increase in arterioles and venules as well as a dense, interconnecting capillary bed. The proliferation of capillary bed renders the overlying skin erythematous.

greater survival areas than acutely raised and delayed flaps (Fig. 25.4).²⁹ Similar studies employing labeled microspheres have demonstrated an increase in flap survival, as well as increased blood flow in the expanded tissue.

Diagnosis and patient presentation

The principles and technique of tissue expansion can be applied in the management of myriad diagnoses with their associated reconstructive dilemmas, therefore patient presentation is variable. Examples of diagnoses where tissue expansion may be utilized include, but are not limited to, traumatic injuries and burns, male-pattern baldness and other forms of alopecia, benign and malignant tumor extirpation defects, breast deformities, and congenital or acquired craniofacial deformities.

Patient and implant selection

Tissue expansion is a protracted procedure that may involve temporary, but very obvious, cosmetic deformity. In general, emotionally stable patients of all ages tolerate tissue expansion well. Noncompliant or mentally impaired patients are poor candidates for this technique. Although not an absolute contraindication, tissue expansion in smokers is associated with a higher risk of complications.³⁰

Tissue expansion is generally best performed as a secondary reconstructive procedure rather than in the acute trauma



Fig. 25.4 Barium-injected radiograph of vessels in a random-pattern skin flap in a pig (A) and an expanded flap in the same animal model (B). A dramatic increase in the vascularity of the expanded flap is evident. (From Cherry GW, Austad E, Pasyk K, et al. *Increased survival and vascularity of random-pattern skin flaps elevated in controlled, expanded skin*. *Plast Reconstr Surg*. 1983;72:680–687.)

period. Expansion can be performed adjacent to an area of an open wound before definitive closure, but such a procedure carries the risks of infection, implant extrusion, and less-than-optimal results. Tissue expansion is best suited to those patients who require definitive, optimal coverage when time is not of the essence.

Implant types

Radovan's initial expander consisted of a silicone prosthesis with two valves, each connected to the main reservoir by silicone tubing.⁷ One valve was used to inject fluid while the other was used to withdraw fluid. Technologic improvements have allowed for the availability of a wide variety of off-the-shelf and custom implants of any shape. These advances have also decreased the incidence of mechanical failure associated with earlier generation implants.

Advances in implant technology include the production of a single valve that allows for fluid injection or removal as well as integrated valves within the expander reservoir. Prostheses that expand differentially into a specific shape, rather than the usual round or rectangular configuration, are also available. Differential expanders have found the most use in reconstruction of the breast, where ptosis and projection of the inferior-most portions of the breast are desired. Low-profile implants that accordion on themselves have been designed to eliminate fold-flaw erosion early in the expansion process. Further modifications of tissue expanders have been made to incorporate surface textures with the theoretical advantages of better tissue adhesion producing decreased rates of implant malposition and capsular contracture.

Expanders with distal ports

Remote filling ports have the advantage of minimizing the risk of implant puncture during inflation. The distal, self-sealing injection port and inflation reservoir are connected to the prosthesis by a length of tubing. This allows the injection port to be placed away from the expander pocket and is advantageous when the overlying skin and soft tissues are thin or when the pocket is too tight to hold an expander with an integrated valve safely.

It is also possible to move the inflation port of a distant reservoir to the exterior of the body. External location facilitates inflation, particularly when the expansion is accomplished by ancillary help or family. Concerns about colonization risk can affect both selection of an implant and management of complications.

Expanders with integrated ports

The inflation reservoir may be incorporated directly into the prosthesis. Such devices have the advantage of avoiding the remote port and its associated mechanical problems. However, the risk of inadvertent perforation of the prosthesis during inflation is higher with integrated valves because the valve and integrated prosthesis can be difficult to palpate. Magnetic and ultrasonic devices can be useful when the valve is difficult to locate and metal-finding devices have been designed. Expander prostheses with integrated valves are particularly popular for breast reconstruction where adequate soft tissue and implant pocket can accommodate the added projection of the injection port.

Self-inflating expanders

Self-inflating expanders have become available largely outside of the United States.³¹ These implants contain osmotic active hydrogel (vinyl pyrrolidone) that causes migration of extracellular water through the silicone membrane of the device resulting in progressive enlargement of the expander. Another type of self-inflating expander employs carbon dioxide for filling. Through an internal carbon dioxide reservoir and valve operated by a remote radio-control, small fixed amounts of the gas are released into the expander resulting in progressive enlargement.

The first such expander was devised by Drs. Austad and Rose. The first generation of osmotic tissue expanders were designed without an envelope allowing rapid swelling within the first few days after implantation resulting in soft tissue ischemia in some cases.⁹ Modifications of these implants to include a silicone membrane which encloses the osmotic tissue expander significantly decreased expansion speed and improved size consistency after complete expansion.³² These implants are currently not approved by the Food and Drug Administration and are not available in the US.

Gas-filled self-inflating expander use in humans was initially reported in 2011 by Dr. Anthony Connell.³³ Seven women with 10 carbon dioxide expanders underwent successful expansion. Subsequent to this proof-of-concept series, Dr. Connell has demonstrated 100% expansion success rate with only minor adverse events and high patient satisfaction.³⁴

Self-expanding devices have the theoretical benefit of continuous or patient-controlled inflation of the prosthesis. Further benefits may include reducing the number of office visits, decreased pain, no need for patient needle sticks, and more rapid expansion. Such prostheses have the downside of potential continued expansion even if overlying tissue becomes compromised.

Incision planning and implant selection

The key to successful expansion is meticulous planning before any incision is made. The proposed type of flap (advancement, rotation, or interposition) that is to be expanded should be carefully planned. In general: the simpler the flap, the less the potential for complication. Ideally, planning is done so that: (1) incisions are incorporated into tissue that will become one margin of the flap; (2) aesthetic units are reconstructed; (3) scars are in minimally conspicuous locations; and (4) tension on suture lines is reduced. The length and position of resultant scars play a major role in determining the overall cosmetic postoperative result. Careful planning allows the prosthesis to be placed through an incision that will both minimize the risk of compromise during flap development and optimize cosmetic reconstruction.

Incisions should be planned to minimize tension on the suture line and risk of extrusion. Tension from the initial inflation on the suture line will be greater when incisions are parallel to the direction of expansion than when they are perpendicular to it. Undermining of the prosthesis should be sufficient enough that the prosthesis can be easily accommodated and the wound can be closed in multiple layers. The inflation valve and tubing should be maintained at a site away from the incision.

Choice of an implant with an external distal port may affect surgical planning. Cultures of implants with external valves

revealed that 82% of these prostheses had colonized the expander capsule and had some infection present which constitutes an infection risk that is slightly higher than that of totally buried prostheses.³⁵ Although patients tolerate this colonization well and experience few complications, external ports are contraindicated when a permanent prosthesis or bone grafts are to be used after expansion is complete.

The size of the implant selected should closely relate to the size and shape of the donor surface. An implant equal to or slightly smaller than the donor area is selected. Because there is minimal risk in hyper-inflating the prosthesis to several times the manufacturer's designated volume, less importance is placed on the implant's specific volume than on its overall base size. On occasion, a custom-fabricated implant may be necessary.

In general, the use of multiple small expanders is better than the use of one large expander. Inflation of multiple prostheses proceeds more rapidly and complications are fewer. Multiple expanders also allow the surgeon to vary the plan for reconstruction after expansion has been achieved.

Because of the variety of functional, medical, and surgical considerations, the choice between an integrated valve and a distal inflation port should be considered on a case-by-case basis, without neglecting plans for infection control and the possible need for nonmedical personnel to inflate the implant.

Implant and distal port positioning

If a remote or distal filling port and reservoir is chosen, it must be placed superficially in subcutaneous tissue, where even an extremely small port is easily palpable under stable skin. To minimize discomfort, it is occasionally possible to position a filling port in an area that is relatively less sensitive. The port should be placed in a location that will not be subjected to pressure when the patient is lying in a position that could put direct pressure immediately over the fill port. Bony prominences are avoided if possible.

Care must be taken to avoid kinking of the tubing so that the injected saline will flow readily to the prosthesis. The prosthesis tubing should avoid the incision through which the implant is placed and should not traverse joints. If placement of an external valve is chosen, the connecting tubing should be tunneled a significant distance from the prosthesis.

Tissue expanders are usually placed beneath the skin and subcutaneous tissue above fascia. When the subcutaneous tissue is thin or the risk of extrusion is significant, prostheses may be placed under muscle.

Treatment and surgical technique

Burns

The use of tissue expansion in the reconstruction of burns, particularly involving the scalp and face, has revolutionized the treatment of burn patients. Because there is almost always inadequate tissue after burns, reconstruction should be carried out after all burns have thoroughly healed and scars have matured. Planning is particularly important in these cases so that a minimum number of suture lines are produced and that these suture lines do not cross aesthetic units. Significant late distortion and contracture may result in excessive scars placed in burned tissue, particularly in the facial area.

Skin that has suffered a partial-thickness burn or that has been scarred by adjacent burns is attenuated and is more amenable to expansion.³⁶ Incisions can be placed in previous scars, but the scar should be mature and relatively thick so that extrusion does not occur. Using an access incision within normal tissue that is peripheral to the burned area further minimizes the risk of extrusion. The principle of using multiple, smaller-volume prostheses is especially appropriate in the burn patient. Perioperative antibiotics and meticulous preparation are always used since the incidence of infection is higher in burn patients.

Tissue expansion in children

Skin and soft tissue are always thinner in children than in adults. These tissues are probably better vascularized but less resistant to trauma. Tissue expansion has a higher complication rate in children than in adults. Rather than using excessively large prostheses or expanding tissue aggressively, accomplishing serial repeated expansions may be helpful in children. This is done with the understanding that major complication risk – particularly extrusion – is more common at the second, third, and fourth serial expansion.³⁷ This is particularly true in the head and neck (with the exception of the scalp). Expansion of the facial areas and neck can be particularly difficult.

After age five, most children are able to adequately cooperate therefore complication rates decrease. In many children, an external reservoir is used to minimize the amount of emotional trauma caused by injections. Application of EMLA to the skin over the buried injection port is also helpful in minimizing discomfort. Small volume inflation at frequent intervals is especially useful in children because the amount of pain generated is considerably less.

As in all cases, planning should be meticulous so that the flaps generated will result as much as possible in reconstruction of anatomic units. With growth, contracture may occur, particularly about the mouth and around the orbits, and revision will be required.

Expansion of myocutaneous, fascial, and free flaps

Myocutaneous flaps are the standard of care for the treatment of large defects, particularly when bone and vital structures are involved. The territories of standard flaps are well described. These territories can be considerably enlarged by placing an expander beneath the standard myocutaneous flap, and an extremely large flap can be developed over a short period. Expansion increases the vascularity of the flap and allows a large, adjacent random area to be carried with the original flap.³⁸ The vascular pedicle of such flaps remains intact and may in fact be elongated, thus allowing flaps to be transferred farther.

Myocutaneous flaps such as the latissimus dorsi and pectoralis major can be expanded to almost double their surface area, allowing coverage of almost any defect of the abdomen or thorax.³⁹ Expanders of up to 1000 mL can be placed beneath such flaps and rapidly expanded. For example, bilateral latissimus dorsi myocutaneous flaps can be expanded and moved to the midline to cover large meningoceles or the vertebral column. In these cases, one edge of the myocutaneous flap is selected for implant placement, and care is taken not to injure

the vascular pedicle. The expanded myocutaneous flap generated can then be transferred as either a pedicled flap or a free flap. Such expanded flaps not only provide coverage of other donor defects but also preserve the function of the muscle.

Fasciocutaneous flaps can be expanded either before or after transposition. When flaps are expanded before transfer, it is best to keep the prosthesis as far away from the pedicle as possible, thus preferentially expanding the random area of the flap. Within 6 months of transfer of these flaps, the random blood supply is usually sufficiently established to allow placement of the expander anywhere under the flap.⁴⁰

Expanded full-thickness skin grafts

Because a donor defect is usually created by harvesting full-thickness grafts, their use is infrequent. The placement of a large tissue expander beneath the donor site can result in a large full-thickness graft that is particularly useful in resurfacing large areas of the face or the entire hand or foot. Expanded full-thickness grafts are extremely resilient and have been shown to grow in children over time. The rate of contracture is significantly less than that of split-thickness grafts.

The best color matches are generated when the full-thickness graft is expanded and harvested as close as possible to the recipient site. The periorbital area and the area around the mouth are particularly well suited to reconstruction with expanded full-thickness grafts harvested from the supraclavicular area. Expanded full-thickness grafts are very helpful in reconstructing defects of the forehead that encompass more than 70% of its surface area. A single full-thickness graft can be harvested from the supraclavicular area or from under the breast fold. Care must be taken that hair-bearing tissue is not transferred to an area that normally has no hair. Expanders with a surface area equal to that of the donor site are placed through peripheral incisions. The prosthesis is then inflated to an adequate volume. After sufficient donor tissue is generated, a template is made of the recipient site and transferred to the expanded donor area. The full-thickness graft is harvested so that it is approximately 10–15% larger than the recipient area, allowing for some contracture. The prosthesis is then removed, leaving the capsule intact, and the donor site closed primarily. Closing of the donor site should be done so that the resulting scar is as inconspicuous as possible. In the recipient site, expanded full-thickness skin grafts require more immobilization than do split-thickness skin grafts. A bolster dressing or, ideally, a VAC sponge dressing is required. The graft is sutured in place, a VAC sponge placed over the graft, and 125 mmHg of negative pressure is maintained for 4 days. Successful take of such grafts placed with this technique is extremely high.

Reconstruction in the head and neck

The head and neck area contains many specialized tissues that must be matched appropriately to achieve optimal aesthetic reconstruction. Aesthetic reconstruction is maximized by mobilization of adjacent local tissues rather than by transfer of distant tissues with poor match of color, texture, or hair-bearing capability. Tissue expansion therefore allows optimal aesthetic reconstruction by use of a similar adjacent tissue area to reconstruct a defect without creation of a donor site.^{11,41}

The skin of the face can be subdivided into five tissue-specific areas:

1. The scalp is unique in that it contains specific hair-bearing qualities that cannot be mimicked by any other tissue of the human body.
2. The forehead is a continuation of the scalp, but it is distinguished from the scalp by its thick skin, large number of sebaceous glands, and lack of hair.
3. The nose is embryologically related to the forehead, so it closely mimics the forehead in color, texture, and sebaceous gland content.
4. The lateral cheek areas, neck, and upper lip have fewer sebaceous glands; the skin is thinner, and the hair-bearing pattern is significantly different in quality and quantity from that on the remainder of the body.
5. The skin of the periorbital areas is extremely thin and pliable, containing a minimal number of sebaceous glands.

There is a limited amount of tissue on the human face, so procedures must be planned carefully and reconstruction accomplished correctly at the first attempt. Correct planning should take into consideration the area and shape of the defect, quality of the remaining tissue of the aesthetic unit, pre-existing scars, and reconstructive needs of other areas of the head and neck. Because of the risk of complications, it is prudent to plan alternative reconstructive strategies before any prostheses are placed. If there is a chronic infection, the presence of fistulas, or the need to reconstruct facial mass/volume, other reconstructive alternatives may achieve a better final result.

Scalp

Tissue expansion is the ideal procedure for the reconstruction of scalp defects (Fig. 25.5).⁴² Expansion of the scalp is well tolerated and is the only procedure that allows development of normal hair-bearing tissue to cover areas of alopecia. The amount of scar and deformity generated is considerably less than with previous procedures such as serial reduction and complex multi-flap procedures. While some animal studies have demonstrated an increase in hair follicles during tissue expansion, our clinical experience suggests that humans do not form a significant number of new follicles. Rather, existing follicles are redistributed to a larger surface area. Because of the finite number of follicles, attempts should be made to redistribute them as homogeneously as possible. To accomplish this, large or multiple expanders, expanding large areas of the remaining scalp, produce the best results. Hair follicles can be separated by a factor of 2 without producing noticeable thinning. The darker the hair, the more visible the thinning is. Individuals who have large defects and require extreme expansion may achieve better results by lightening the hair color with dyes.

Although there is considerable overlap in the vascular territories of the scalp, the incorporation of one or more major vessels of the scalp optimizes reconstruction. Flaps should be well vascularized to ensure maximum growth of hair. Planning is therefore of importance, as is consideration of scar and previous areas of trauma. Advancement or rotation flaps achieve the best results, particularly when the anterior hairline is reconstructed. Simultaneous expansion and mobilization of the forehead may also help achieve a normal hairline.

Previous scars and incisions can be used for placement of the prosthesis. Once the galea is encountered, dissection can proceed widely with a blunt dissector. It is not unusual to

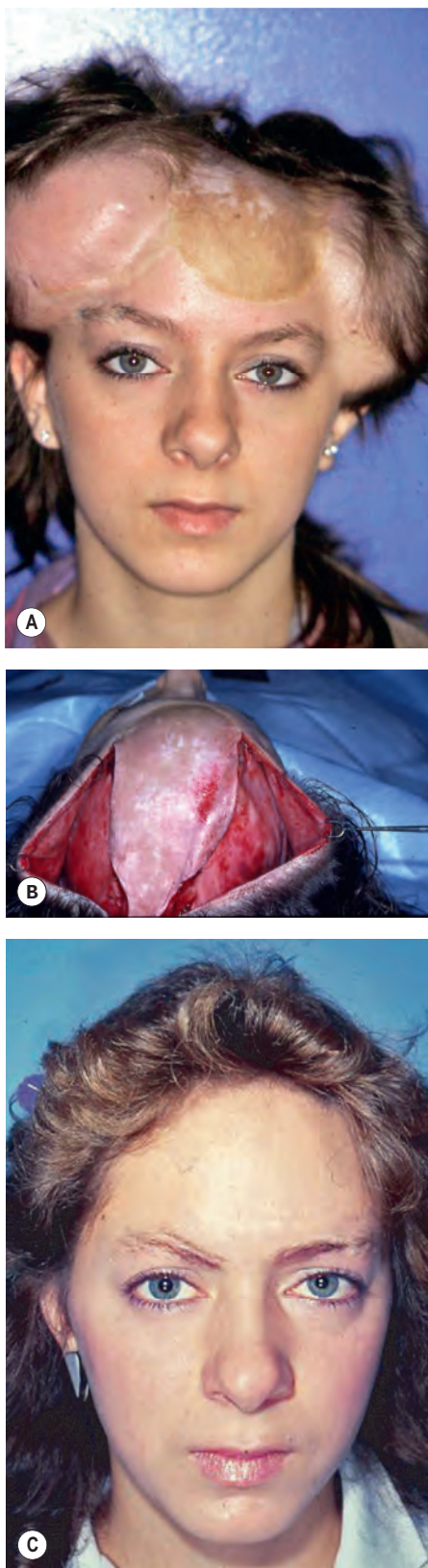


Fig. 25.5 (A) Young woman with avulsion injury to the right scalp, which had been covered with a transposition flap from the left scalp that resulted in a scalp and forehead skin graft. Two expanders were placed, one on either side, encompassing as much of the hair and forehead as possible. (B) Expanders removed and advancement flaps ready for repositioning. (C) Patient shown postoperatively with a normal hairline, normal brow, and normal hair-bearing scalp.

mobilize most of the remaining scalp so that the prosthesis is well accommodated. Individual pockets are not necessary for multiple expanders, but care should be taken to fix the inflation reservoirs so that they do not migrate into a common pocket. Prostheses with incorporated inflation reservoirs can also be used, but patients often find them bulky and uncomfortable. Inflation reservoirs can be placed at the vertex of the scalp or in the forehead but care should be taken not to place them where pressure is applied during sleep.

Expansion of the scalp is initially uncomfortable. It is better to use frequent small saline injections than to use infrequent large injections. After several weeks, the scalp loosens, and large amounts of saline can be infused without difficulty. Most scalp expansions can be accomplished in 6–8 weeks, particularly when multiple expanders are used.⁴³

Once adequate expansion has been achieved, the prostheses are removed through the incisions through which they were originally placed or at the margin of the flap to be moved. Flaps should be designed for advancement, transposition, or rotation. Every attempt should be made to minimize transection of the major vessels of the scalp as this will allow faster healing and better regeneration of hair follicles. Removal or cutting of capsule and galea should be avoided in order to preserve blood supply. Large areas of the scalp are mobilized and positioned by temporary staples. Dog-ear deformities created with flap inset are left in place because they subside over time. The wounds are then closed.

It may be impossible to gain an adequate amount of tissue with one expansion when large areas of the scalp must be resurfaced, in which case serial expansion is used (Fig. 25.6). After the initial expansion, flaps are advanced as far as possible. Lesions or areas of alopecia are excised only after the flap has been advanced. The expander is then left in place under the flap and, after several months, the scalp is re-expanded. Adults tolerate three or four sequential expansions without difficulty. The skin of infants and children may thin excessively after two expansions and an interim period of 8–12 months is optimal for a later expansion.

In growing children, scars frequently widen over time. These require revision when they become a cosmetic problem, optimally after 16–18 years of age. Scalp that has been vigorously expanded may lose some hair follicles, but these usually regrow hair. Twelve months should pass before any areas of alopecia are considered permanent.

Some erosion and depression of the skull may be seen in children radiographically and, occasionally, clinically. Expansion should best be delayed in children until they are approximately 1 year of age. By this time, the skull is solid enough that significant erosion is not a cause for concern. Long-term studies have demonstrated no detrimental growth of the skull in children who have undergone scalp expansion in infancy (Fig. 25.7).

Male-pattern baldness

Tissue expansion can be used to develop hair-bearing flaps that will replace skin that is affected by male-pattern baldness.^{44,45} Expansion allows the homogeneous distribution of the remaining hair follicles and reduces the tension that can be caused by excision of scalp.

In patients with vertex baldness, the remaining temporal and occipital scalp can be expanded for 2 months. Expanders

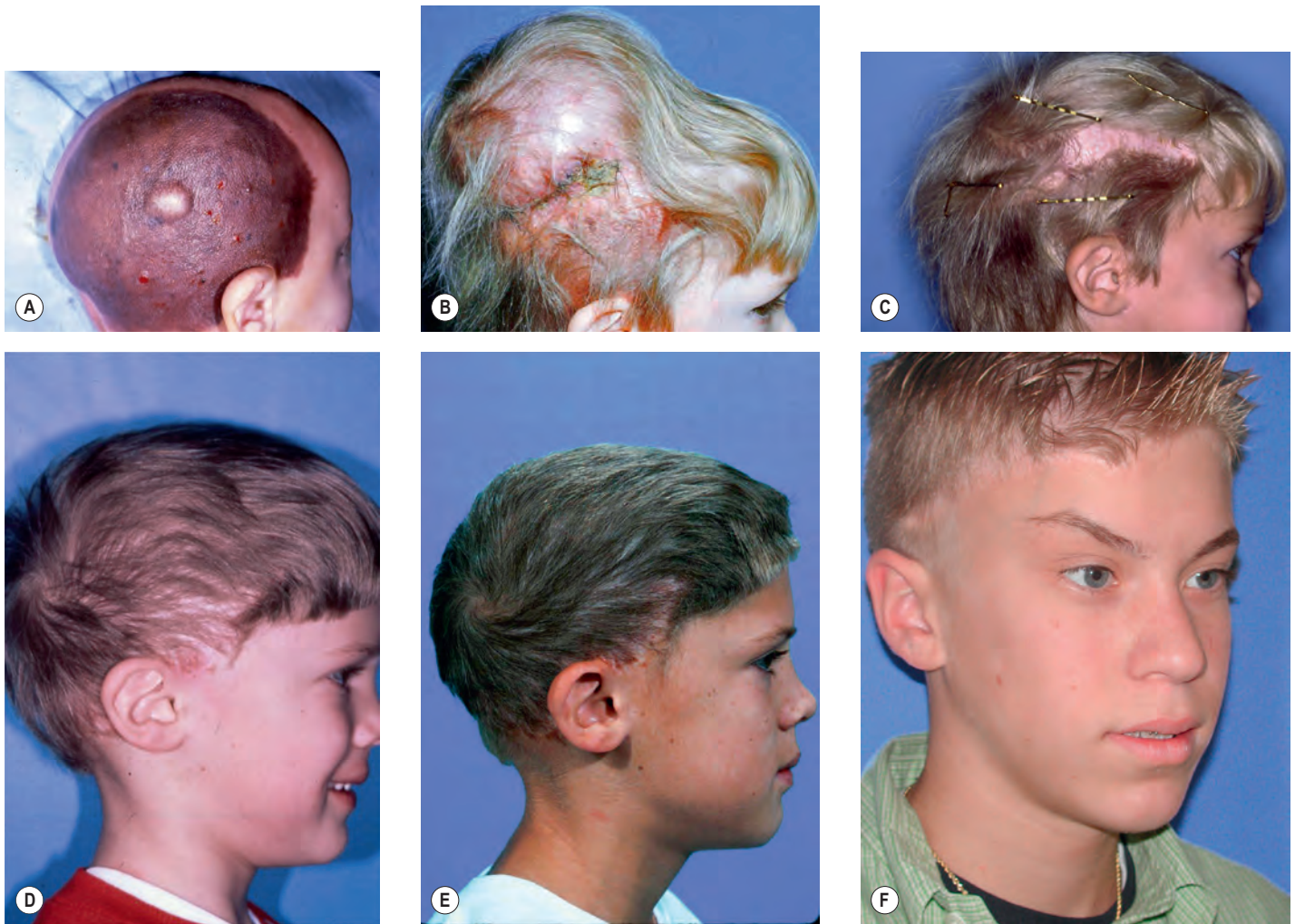


Fig. 25.6 (A) Child born with a giant hairy nevus occupying one-third of the scalp. (B) The remaining normal scalp was expanded, allowing removal of more than half of the lesion. (C) The original expander was left in place and 4 months later re-expanded, generating tissue that allowed removal of the remaining lesion. (D) The patient is shown 1 year after expansion. (E) The patient 10 years after expansion with stable hairline and normal hair distribution. (F) Patient shown at age 18. No revisions have been required.

are placed through incisions that would normally be used for scalp reduction. Cosmetic deformity during this process may be significant after the first several weeks. At the second procedure, the scalp is advanced as far as possible and the area of alopecia removed.

Patients who are unable to accept the deformity that occurs with single large expansions can be serially expanded and undergo serial scalp reduction. In these patients, the prosthesis is inflated until deformities become visible. The expanders are deflated and the hair-bearing flaps advanced as far cephalad as possible. The prostheses are left in place, and a second or third expansion is carried out until the entire bald area is removed.

Expansion can also be used to significantly increase the size of standard transposition flaps used in the management of male-pattern baldness. Anterior baldness that affects the hairline can be modified into a new, natural-looking hairline with Juri transposition flaps. However, these flaps are limited in size and may require multiple delays to ensure adequate hair viability.⁴⁶ Expanders placed beneath the temporoparietal area can dramatically increase the size of Juri flaps and increase their safety. Bilateral flaps, one transposed behind the other, will cover the entire forehead and a significant portion

of the scalp behind it. The bilateral advancement-transposition flap is especially efficacious in transposing a large amount of hair to the forehead.⁴⁷

Forehead

The forehead is anatomically and histologically identical to the scalp except for its different numbers of sebaceous glands and hair-bearing follicles. Reduction or increase of the surface area of the forehead by 20–25% is not usually readily apparent after appropriate hair styling. By expanding the scalp in conjunction with expanding the forehead, better symmetric brow positioning is achieved while maintaining the normal hairline.

In individuals with very high hairlines, the scalp can be expanded posteriorly and brought forward to the junction of the forehead and scalp. Generally, a lateral movement of scalp tissue is less visible postoperatively. When defects involve tissue lateral to the orbit, expansion of the cheek area with cephalad movement of the exposed tissue may be helpful. The temporal hairline and the lateral hairline that lies anterior to the ear can be reconstructed with an advancement or transposition of a scalp flap.

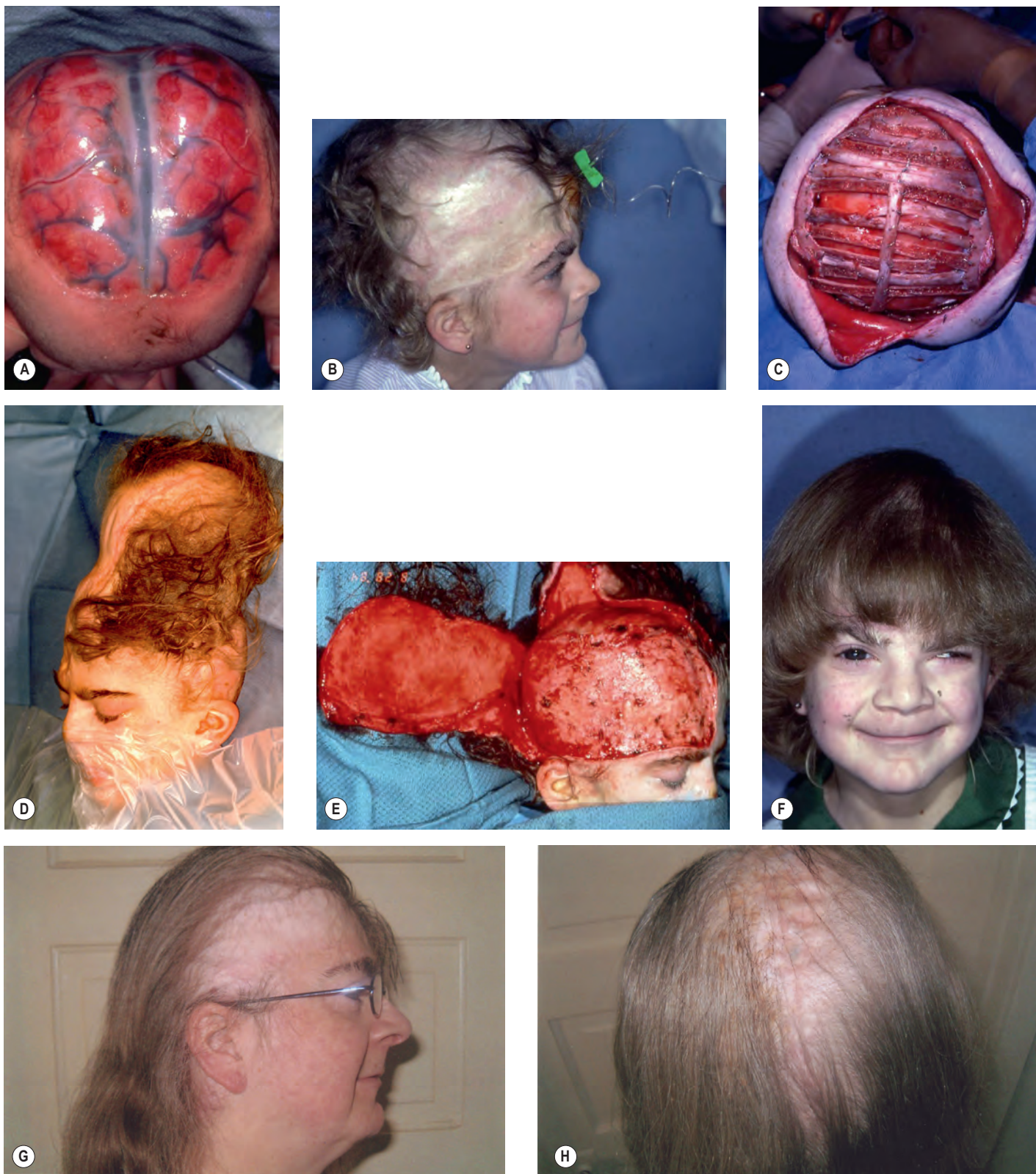


Fig. 25.7 (A) An infant born with severe aplasia cutis congenita involving the scalp, skull, and derma that left exposed brain. (B) The brain was covered immediately after birth with two, large, scalp-forehead advancement flaps. Absence of the cranium prevented the patient from attending school. (C) At age 4 years, the flaps were separated from the underlying brain; a reinforced polyethylene sheet was secured to the cranial defect, an expander was placed over the sheet, and the scalp was expanded for 3 months. (D) The cranium was reconstructed with multiple split-rib grafts within the expanded capsule. (E) One year later, the scalp was re-expanded to more than 1000 mL over the reconstructed cranium. The skin graft was excised and the scalp and forehead flaps were repositioned appropriately. The reconstructed skull suffered no ill effect during the re-expansion. (F) Patient shown 1 year after reconstruction. (G) The patient at age 36 with an intact skull, normal scalp, and minor alopecia. (H) Posterior scalp showing thinning of hair-bearing tissue, but a resilient, pliable scalp over an intact cranium. (From Argenta LC, Dingman RO. Total reconstruction of aplasia cutis congenita involving scalp, skull, and dura. *Plast Reconstr Surg.* 1986;77:650–653.)

Prostheses are usually placed in the forehead through an incision in the scalp. The prostheses are placed beneath the frontalis muscle because this plane is safe and a well-vascularized flap can be developed. Multiple expanders are usually needed both to generate adequate tissue to be mobilized and simultaneously to allow the brows to remain in an appropriate symmetric position. Expansion is at first difficult and uncomfortable, but as in the scalp, the expansion proceeds rapidly after several weeks. Flaps may be developed in any direction but are usually simple advancements. The adjacent scalp should be mobilized at the same time so that a normal hairline can be reconstructed.

Expansion of the forehead is useful in many craniofacial anomalies with low hairlines. Expansion of the remaining forehead is accomplished and moved in a cephalad direction. The intervening hair-bearing scalp is excised. Fixation of the

expanded forehead to the underlying skull with small screws reduces the amount of retraction.

If the entire forehead must be reconstructed, the optimal choice is the use of an expanded full-thickness graft from the neck. These grafts must be secured in place with negative-pressure devices for at least 4 days.

Lateral face and neck

The type of skin on the lateral facial areas and neck is essentially the same. This skin has hair-bearing potential and is relatively thin, but contains numerous oil and sebaceous glands. It is much thinner than skin on the forehead and nose.

A large Mustardé expanded rotation flap can be developed on the neck for use in facial reconstruction. In children, there is a higher risk of extrusion problems in the expansion of this



Fig. 25.8 (A) An infant with a giant hairy nevus of the face. (B) The neck and lateral face were expanded by placing a prosthesis through an incision in the nevus. An expanded Mustardé cheek rotation flap was rotated as an aesthetic unit over the lateral face. (C) The patient at 5 years of age. (D) The patient at 18 years of age with minimal scars that are easily amenable to makeup. (E) Lateral view demonstrating no ectropion and an aesthetic reconstruction.



Fig. 25.9 (A) Young man who sustained extensive burns over the face, but in whom the neck was largely spared. (B) Bilateral large expanders were placed in the neck and the entire neck and upper chest were expanded dramatically. (C) The area of burned skin over the lower face was excised and the neck flap advanced superiorly. The capsule was secured firmly to the muscle on the lateral commissures to minimize later distortion of the mouth. (D) The patient 2 years later. The upper lip has been reconstructed as an aesthetic unit from hair-bearing, temporoparietal flaps.

area of the face (Fig. 25.8). In adults, such reconstruction can be accomplished with relative ease. The flap is based inferiorly and medially.

The prosthesis is inserted through a preauricular facelift-type incision. The platysma should not be incorporated because doing so exposes the marginal mandibular nerve to trauma and restricts flap advancement. Distal reservoirs are usually placed in the neck or behind the ear. The prosthesis is then inflated as tolerated by the patient. Despite placement of the prosthesis over the carotid artery and jugular vein, few complications have been encountered. Once an adequate amount of tissue has been generated, the Mustardé flap is elevated. This is done through a preauricular incision that is carried in front of the hair-bearing scalp and then on to the lateral orbital area above the lateral canthus. The flap is then rotated medially and superiorly to cover the areas of the cheek that require resurfacing. In general, it is best to rotate this flap and secure it in place with temporary staples before the recipient area is excised. It is best not to carry the medial scar in this flap beyond the lateral commissure because scars below that feature tend to distort the mouth. The flap is suspended both medially and laterally at a level above the canthus which minimizes the development of later ectropion. If coverage is required for the periorbital area, this is done as a separate aesthetic unit graft, usually a full-thickness graft from the supraclavicular area.

The lower half of the face and the neck are aesthetically the same unit. Hair distribution, sebaceous gland density, and skin thickness are similar. Defects of the lower face and neck can be interchangeably reconstructed by expanding either the lower face or the neck. Most frequently, the neck is expanded and the flap advanced into the lower face. If necessary, bone grafts that are placed beneath the expanded flap can reconstruct the mandible and maxilla. The prosthesis should be placed in the neck superficial to the platysma muscle. Once an adequate amount of tissue is generated, the flaps can be brought superiorly to cover the lower edge of the face, medially to cover the central portion of the neck, or laterally in the neck as needed (Fig. 25.9). In cases where flaps are brought from the neck into the face, it is important to secure the flap with permanent sutures to the deep muscles at the commissures of the mouth. If this is not accomplished, oral incontinence may develop later. Form-fitting neck collars may be necessary to secure the expanded flap in place over the neck after a portion of it has been brought on to the face.

Nose

Reconstruction of major defects of the nose, including total nasal reconstruction, may be facilitated by pre-expanding the forehead skin. Before the use of tissue expansion, having both

inadequate amounts of tissue and difficulty closing the forehead could be anticipated. However, now, when total nose reconstruction is performed, expansion of the entire forehead with a 400–600-mL prosthesis generates an adequate number of large, well-vascularized flaps to accomplish both total nose reconstruction and closure of the donor site. Because the color and texture of the forehead are ideally suited to reconstruction of the nose, this procedure makes reconstruction of any nasal defect possible.

Any of the standard forehead flaps can be employed in conjunction with expansion. If reconstruction of the nasal lining is also necessary, expansion of a forehead or Converse scalping flap develops enough tissue to allow folding of the expanded tissue on itself.

The supraorbital and supratrochlear vessels are located by Doppler examination, and the nasal flap is based on the location of either of these axial vessels. Prostheses are best placed beneath the frontalis muscle through an incision above the



Fig. 25.10 (A) This woman had her nose resected for a mucosal melanoma. Three years later, reconstruction was begun by placement of a 450-mL expander in the forehead. (B) At the second procedure, the infrastructure of the nose was made with a cantilever bone graft and bilateral, conchal cartilage grafts. (C) The forehead flap was turned down in the subperiosteal plane to the level of the medial canthus. (D) The distal third of the flap was markedly thin so that the skin could be turned on itself to recreate the nasal lining. (E, F) The patient 11 years after reconstruction with a functional breathing nose. No further modifications have been required in the succeeding 24 years.



Fig. 25.11 (A) A complex midface giant hairy nevus in a newborn. Reconstruction was undertaken in multiple stages at 2.5 years of age. (B) Bilateral expanders were placed in the neck area to reconstruct the lateral face and a third expander was placed in the lateral thoracic wall to generate an expanded, full-thickness skin graft. (C) Bilateral Mustardé cheek flaps were advanced as aesthetic units. Note that the nevus outside the anatomical aesthetic unit was left in place to be resected later. (D, E) The forehead was excised and a full-thickness skin graft was harvested from the expanded right thoracic wall.

hairline. At the second procedure, the expander is removed and the flap, including the capsule, is rotated inferiorly. Approximately 2 cm above the supraorbital rim, the posterior capsule is incised, and development of the flap is continued in a subperiosteal plane. This allows further mobilization of the flap into the orbit and dissection may continue almost down to the canthus.

Having sufficient bony and cartilaginous supporting structures of the nose is critical to avoiding contraction of the

expanded tissue. Early experience in use of expanded forehead tissue was unsuccessful because the underlying bony and cartilaginous structure was not adequate. A cranial bone or rib graft is taken to reconstruct the dorsum of the nose. This is either secured to the remaining nasal bone or attached by a plate to the skull. The nasal cartilage is reconstructed bilaterally with cartilage from the conchal bowl. Thinly carved rib cartilage is also useful if the ear cartilage is inadequate. Nasal stents are used for 3–4 months to maintain a patent airway



Fig. 25.11, cont'd (F) The expander in the lateral thoracic area was left in place and re-expanded. In a later procedure, the remaining areas of nevus in the nasolabial folds on each side were excised. The entire periocular and nasal area was then excised and grafted with full-thickness, expanded graft. **(G, H)** The patient 5 years after reconstruction with a stable result. **(I–K)** The patient at 21 years of age. Note that the face has grown normally and symmetrically and that facial nerve function has been maintained. The patient is able to hide remaining scars with minimal makeup.

while the flap matures. The forehead flap is divided and inset approximately 2 weeks after rotation. Some swelling and contracture of tissue may occur, but major touch-ups are infrequently needed (Fig. 25.10).

Ear

Most cases of microtia and traumatic ear deformities can be reconstructed without expansion. Expansion is helpful when skin and soft tissue are insufficient for reconstruction. As with all ear reconstructions, a child should be approximately 7 years of age before reconstruction is begun. A custom or rectangular expander is placed beneath the remaining non-hair bearing tissue that is adjacent to the ear remnant. The

prosthesis is then expanded and left in place for approximately 3 months. This allows both significant thinning of the overlying skin and tissue maturity that will together result in minimal secondary distortion due to contracture.⁴⁸

The expander is best placed through an incision in the postauricular hair-bearing tissue, preserving the temporoparietal fascia for possible later needs. Once adequate tissue has been generated, the framework is reconstructed with carved costal cartilage. Some exaggeration of the bulk of the infrastructure minimizes distortion because it conforms to the cartilage. Silicone and other synthetic frameworks give excellent initial results, but they are fraught with late complications. In general, autologous tissues are recommended for ear reconstruction.

Periorbital area with expanded full-thickness grafts

The periorbital area contains skin that is soft and pliable. It contains few glands and no hair. Unfortunately, little tissue in the periorbital area can be expanded or moved easily. When large areas require reconstruction, full-thickness skin grafts from expanded donor sites are recommended. Replacement of aesthetic units – the entire periorbital area or the upper or lower lid – gives the best result (Fig. 25.11).

The supraclavicular area contains soft pliable skin that mimics orbital skin. Therefore, this is a good site for expanding, templating, and harvesting tissue subcutaneously, above the platysma. After harvesting, the expanded skin graft is thinned to dermis and sutured to the recipient site (see section on [expanded full-thickness skin grafts](#)). Long-term results have been remarkable in that this tissue grows with children, scarring is minimal, and secondary reconstruction is infrequent.

Reconstruction in the breast, chest, trunk, and extremities

Post-mastectomy breast reconstruction

Tissue expansion was introduced by Chemar Radovan in 1982 to facilitate breast reconstruction in post-mastectomy patients because these patients were found to have insufficient chest wall tissue for placement of the implant.⁷ Originally, the expanders were placed subcutaneously, but results from these reconstructions tended to be firm and round with a less-than-ideal cosmetic appearance. As the procedure became more widely accepted, surgeons preferred subpectoral and submuscular placement of implants. Breast reconstruction techniques have continued to evolve over the last 40 years and, with refinements in the techniques for autologous tissue transfer, the aesthetic standards for breast reconstruction have increased. Tissue expansion allows ideal color and texture match of the reconstructed breast with the remaining chest wall because the breast is generated from existing chest wall skin. Tissue expansion is a much simpler option for breast reconstruction than the more complex procedures used in autologous tissue transfer.

Use of tissue expansion and breast implants remains the most common method for post-mastectomy reconstruction in the US. Four factors account for widespread use of this technique: (1) continued refinements in surgical technique for mastectomy; (2) preservation of the pectoralis major muscle and its innervation; (3) less radical excision of skin with skin-sparing mastectomy; and (4) preservation of the inframammary fold. Because of these practical techniques, more reconstruction cases in patients with qualitatively good chest wall skin and soft tissue are suited to expansion techniques.

Placement of a tissue expander for breast reconstruction is a simple, straightforward procedure. In the case of immediate reconstruction, it adds little operative time after mastectomy and does not prolong the post-mastectomy hospitalization. Delayed reconstruction with a tissue expander can be done as an outpatient procedure or with minimal hospitalization. Furthermore, it is ideally suited to both elderly patients and those who wish to have a minimal postoperative recovery.

Breast reconstruction with the tissue expansion technique usually requires two operative procedures. In the first procedure, the tissue expander is placed through the original

mastectomy scar, thus avoiding additional scarring. Removal of the tissue expander and placement of the permanent implant are also accomplished through a straightforward approach and can be done under general or local anesthesia in an outpatient setting. However, if the expander is less than ideally positioned, the second procedure will be more complicated, requiring capsulotomy or capsulectomy. The reconstructed breast will experience some shifting and settling after placement of the permanent implant, so it is usually best to delay nipple reconstruction for several months.

Recreation of the inframammary fold and natural breast ptosis remains a difficult aesthetic goal. The location of the expander – whether it is better placed subpectorally or entirely submuscularly – is therefore a frequently debated topic. The use of acellular dermal matrix (ADM) to cover the lower pole of the implant expander was introduced in 2005⁴⁹ and has gained in popularity in recent years because it obviates the need for dissection of the serratus anterior. This results in less implant displacement during expansion.

The breast expander device

The original breast expanders were smooth-walled silicone devices with a remote port. Placement of the remote valve often proved tedious and, if not perfectly placed, resulted in mechanical filling difficulty. More recently, expanders with integrated valves have become the expanders of choice in breast reconstruction.^{50,51} The valve is located in the upper pole of the breast. Because an inflation needle can puncture an expander, the valve is easily palpable and has a metal backing to prevent injury to the attached expander. The integrated valve avoids the need to create a separate lateral pocket and subcutaneous tunnels for the connecting tube. It avoids the complications associated with a distal port, including rotation and extrusion of the port, and mechanical problems related to the connecting tubing such as kinking and leaking.

The textured silicone implant has been an important advance in breast reconstruction with tissue expansion. A textured surface enables tissue ingrowth and adherence of the capsule, which, in turn, immobilizes the implant. It is imperative that the textured expander be ideally positioned. The immobility of the textured implant enables development of two aesthetic benefits: a more anatomic expansion of the overlying tissue and more expansion in the inframammary fold area that helps establish a fold with some degree of ptosis.

Expander devices are generally described as round or anatomic. Each device is designed to allow for a more natural breast reconstruction by providing unique differential expansion of the upper, middle, and lower poles of the breast. In our experience, however, two other factors determine the final outcome more than the expander shape does: the quality of the skin and subcutaneous tissue and the preservation of the inframammary fold after mastectomy.

Immediate breast reconstruction

The inframammary folds should be marked with the patient sitting in an upright position before general anesthesia is induced for mastectomy and placement of the expander. The mastectomy should be accomplished in a fashion that maximizes local control, with careful attention, however, to preservation of skin and subcutaneous tissue, especially in the inframammary fold area. In recent years, with the

optimization of skin-sparing mastectomy and development of nipple-sparing mastectomy, general surgeons are much more conscientious in preservation of the skin. If too much skin is spared, the plastic surgeon will need to trim excess skin that could cause dog-ears and sagging; this is done after placing the expander.

After completion of the mastectomy, the expander is placed in one of three locations, depending on the surgeon's preference and experiences. These are the total submuscular position, the subpectoral (dual-plane) position, and the subpectoral position with supplementation with an ADM.

Complete muscle coverage is more important in immediate than in secondary breast reconstruction because it completely isolates the implant from the overlying mastectomy wound. Should there be skin necrosis with a loss of mastectomy flaps, wound dehiscence, delayed healing – especially in previously irradiated chest walls – or cellulitis, a totally submuscular implant may be salvaged, whereas a partially submuscular implant will be lost.

After placement of the implant by one of these three methods, suction drains are placed in the subcutaneous space and in the axilla if a lymph node dissection has also been completed. The wounds are closed in layers and the expander filled with enough fluid to obliterate dead space, but avoiding excessive tension on the wound closure.

Submuscular position

When the submuscular position is used for expansion, a submuscular pocket is dissected for placement of the tissue expander. The muscle incision can be made in one of two locations. If a musculofascial layer has been preserved after mastectomy, the incision can be made parallel to the pectoralis major fibers. Using sharp and blunt dissection, the pectoralis major muscle is lifted off the underlying chest wall and the pectoralis minor muscle. Dissection is continued inferiorly beneath the origin of the rectus abdominis muscle and laterally beneath the serratus anterior muscle.

Alternatively, an incision can be made at the lateral border of the pectoralis major or parallel to the fibers of the serratus anterior muscle. This dissection is continued down to the rib, and from the lateral position, a pocket is dissected inferiorly, superiorly, and medially, lifting the pectoralis major origin off the rectus abdominis muscle and the origin of the serratus anterior muscle.

It is important to avoid dissecting the serratus anterior muscle too far laterally, regardless of the location of the muscle incision, for this would allow displacement of the implant into the axilla. If the fascia at the junction of the pectoralis major and rectus abdominis muscles has been violated during mastectomy, complete submuscular closure can be difficult. In general, a small exposure of the implant is of no consequence. A large exposure can be covered with a transposition or rotation of anterior rectus abdominis fascia.

Subpectoral (dual-plane) position

Only the upper two-thirds of the expander in the subpectoral (dual-plane) position is covered by muscle. Advantages include less postoperative discomfort and less discomfort during expansions. Criticisms of this technique include the risk of upward migration of the pectoralis major, which results in even less coverage of the lower portion of the implant. If

there is wound breakdown at the mastectomy incision, the implant, rather than muscle, will be exposed.

The inferior border of the pectoralis major is identified, the pectoralis fascia is incised if it has been preserved, and the muscle is elevated while preserving the origin of the serratus anterior and rectus abdominis muscle. The expander is introduced so that it lies in a dual plane with its upper pole covered by muscle and its lower pole solely by subcutaneous tissue.

Subpectoral position with an ADM

An ADM can be used to extend the subpectoral pocket, creating a hammock effect below the implant that provides an aesthetic inferior pole and inframammary fold, as well as soft-tissue coverage (Fig. 25.12).^{51–56} The hammock, or sling,

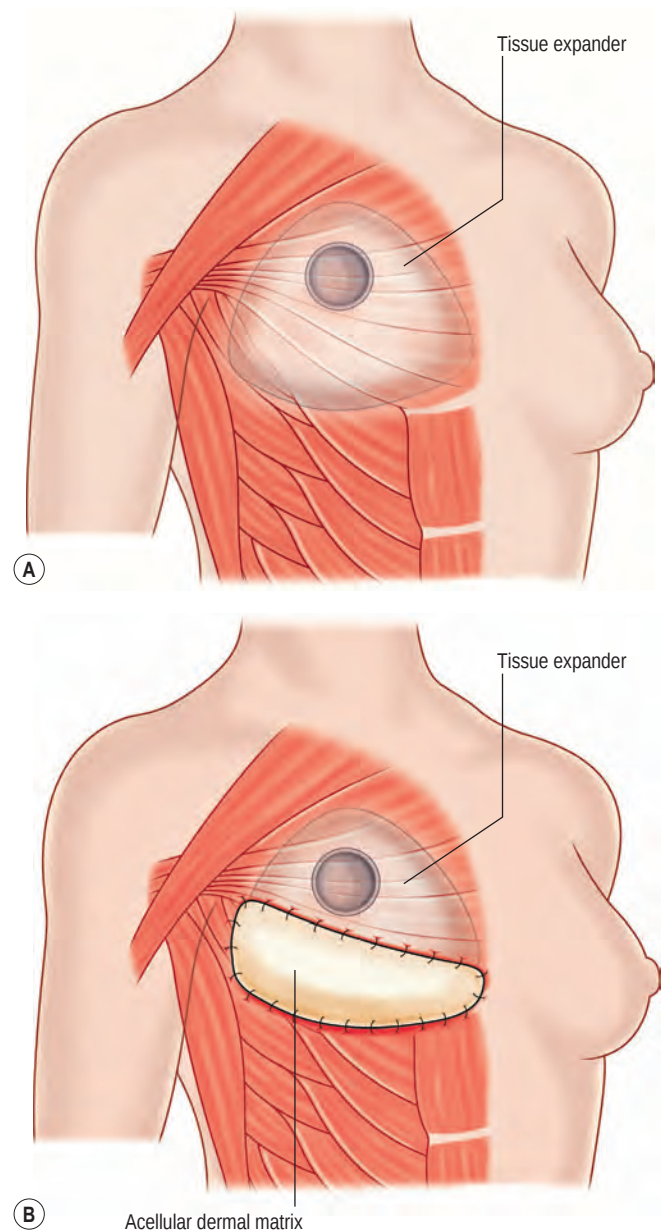


Fig. 25.12 (A) Tissue expanders for breast reconstruction are usually placed beneath the pectoralis and serratus muscles. **(B)** It is possible to place the prosthesis under the pectoralis major, where the muscle covers only the top half of the prosthesis, when a dermal matrix is sutured to the lower half of the pectoralis muscle and the chest wall to cover the lower half of the prosthesis.

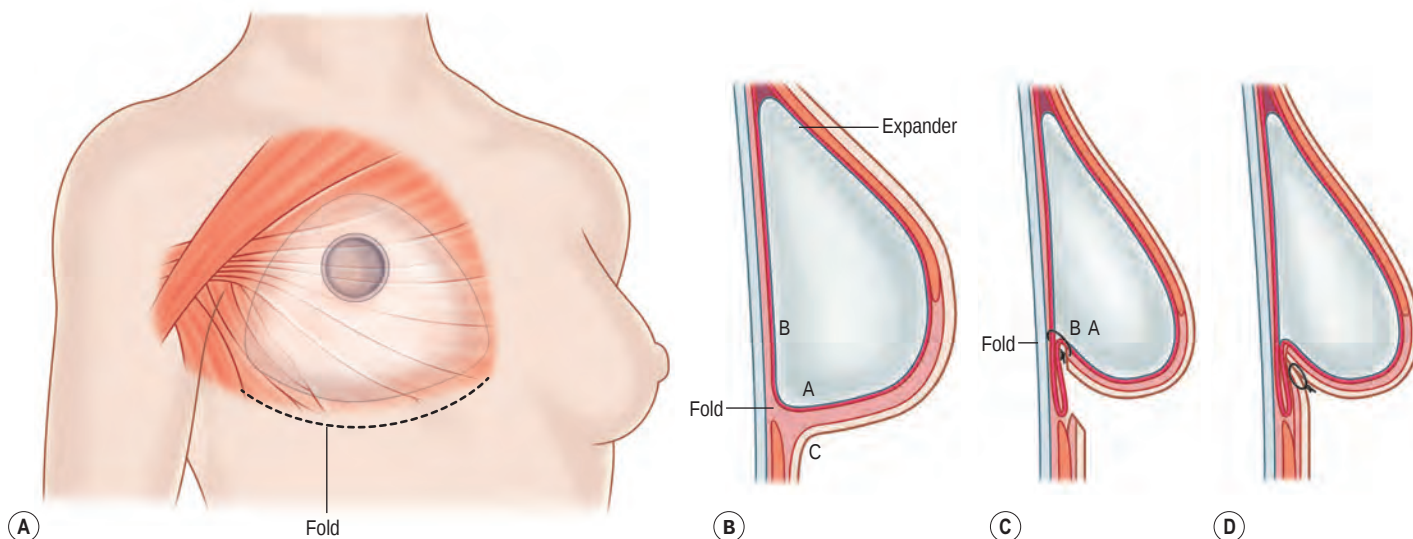


Fig. 25.13 The technique of designing a ptotic breast by moving the inframammary fold. **(A)** The prosthesis is over-expanded to make an excess amount of tissue. **(B)** The position of the desired breast fold (point B) is determined on the thoracic wall. **(C)** Through an inframammary incision at point C, the expander is removed and a permanent device is placed. The skin and soft tissue (point A) are moved superiorly and sutured to point B. **(D)** The abdominal wall is undermined above the fascia and advanced into the inframammary defect.

holds the expander in place, minimizing the risk of downward migration of the implant. Further, the expander is less restricted than when it is completely submuscular, so expansion can progress more rapidly before placement of the permanent implant. In non-irradiated patients, human acellular dermis is re-vascularized and remodeled into the host tissues.⁵⁷ A number of human ADMs are commercially available. The ADMs are expensive and their cost must be considered when planning the best reconstructive course. Another disadvantage of using ADMs is that they also promote serous drainage, requiring drains to be maintained until serous drainage is less than 30 cc/day.

The pectoralis major muscle is elevated as described above. A sheet of ADM is sutured to the fascia overlying the rectus abdominis muscle at the planned inframammary fold. The size of the matrix is determined by the diameter of the chest wall and elasticity of the chosen dermal matrix. Typical sheet sizes vary from 4×12 cm to 6×16 cm. The expander is introduced beneath the pectoralis superiorly and the ADM inferiorly and the muscle and superior edge of the ADM are approximated. Drains are placed to accommodate serous drainage. If there is breakdown of the mastectomy wound, the underlying matrices will become exposed. Our preferred management of this complication is early excision of ischemic skin and re-closure of the wound.

Delayed breast reconstruction with tissue expansion

As with immediate reconstruction, it is important to mark the inframammary fold and the extent of undermining while the patient is sitting in an upright position before induction of anesthesia. The tissue expander may be placed in one of the three pockets described above for immediate placement after mastectomy.

Inflation follows the general plan for expansion as previously described. Inflation of the expander is initiated 10–14 days after placement. The patient returns weekly or biweekly for serial percutaneous inflations. A 23-gauge butterfly needle is used with a distal port and a 21-gauge needle is used

with an integrated port. Care is taken not to overinflate the expander, causing unnecessary discomfort. The expander should be inflated until the overlying skin and subcutaneous tissues feel firm. If the patient experiences significant discomfort, saline is withdrawn until the patient is comfortable. With each inflation, the overlying skin frequently becomes hyperemic, but the problem usually resolves after inflation has been completed. After volumetric symmetry with the opposite side is achieved, hyperinflation of the expander is often carried out. If a large amount of ptosis is to be developed or extensive repositioning of the breast is necessary, additional hyperinflation may be required. Expanders may be left in place for many months or even years before being exchanged for permanent implants and this principle is also applied in the management of adolescent hypomastia.¹³

Repositioning of the inframammary fold can influence breast ptosis and definition. Increased ptosis is created by infolding and uplifting the expanded tissue and advancing a lower abdominal flap.^{58,59} After removing excess saline to determine the appropriate, symmetrical volume of the reconstructed breast, the inframammary fold is moved up or down so that the apices of the breasts are at an equal level. The new position of the fold is marked so that the reconstruction can be accomplished through an incision at the desired inframammary fold (Fig. 25.13). The capsule is left intact unless the prosthesis needs to be repositioned. Stable reconstruction of the inframammary fold can be achieved by tacking the interior capsule to the posterior chest wall capsule at the same level where the earlier, symmetrical marking was made. The abdominal skin is undermined above the fascia and is advanced superiorly into the inframammary cleavage to close the posterior wall defect (Fig. 25.14).

Tissue expansion in cases of chest wall irradiation

Studies suggest that previous chest wall irradiation negatively affects success with tissue expansion and subsequent implant placement.^{60,61} The complication rate due to infection, extrusion, and wound complications is higher. Furthermore, the

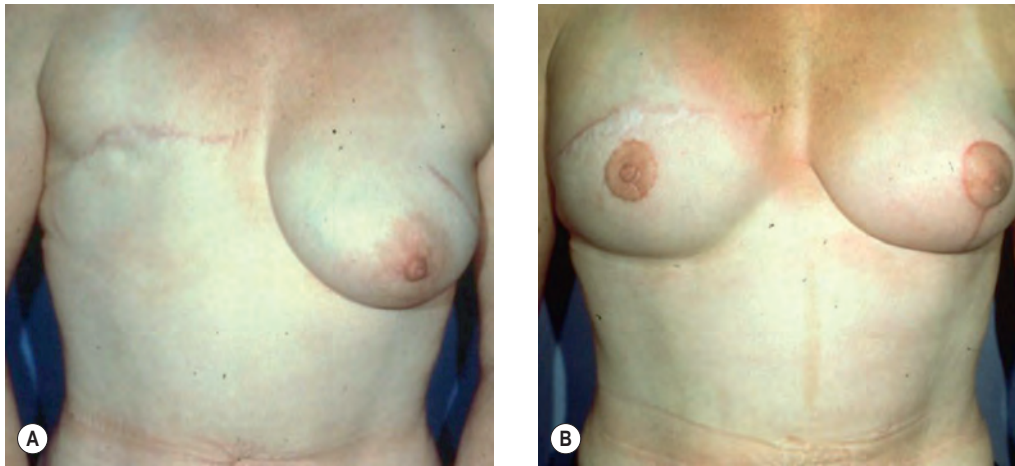


Fig. 25.14 (A) A patient after modified radical mastectomy with preservation of the pectoralis muscle. (B) An expander was placed beneath the pectoralis and serratus muscles and then gradually over-expanded. At a second procedure, a permanent implant was placed and a ptosis procedure was performed on the opposite side.

final aesthetic result is frequently compromised by capsular contracture.

Two groups of patients are probably best managed with autologous tissue transfers instead of with tissue expansion. They are those undergoing: (1) mastectomy for recurrence of disease after previous lumpectomy and radiation; and (2) secondary reconstruction after mastectomy and radiation. In selected patients with excellent-quality chest wall skin and soft tissue, tissue expansion may be considered even though the incidence of complications and a compromised aesthetic result are high.

Chest wall irradiation treatment is increasingly frequent in post-mastectomy patients. A large number of women who have undergone placement of a tissue expander at the time of mastectomy now have to deal with postoperative radiation. There is no consensus at this time on how to manage these patients. Alternatives that have been presented include the following:

1. Continue expansion until the time of irradiation, but cease inflating the expander during and for several months after irradiation; then resume expander inflation once the radiation dermatitis has resolved and follow with placement of the permanent implant.
2. Complete expansion and exchange with the permanent implant and then proceed with radiation.
3. Remove the fluid in the expander, initiate and complete radiation therapy, and then re-inflate the expander once tissues have begun to heal.
4. Remove or maintain the tissue expander and make plans for autologous tissue reconstruction after radiation is complete.

Despite the above risks, more than 50% of patients are reported to have satisfactory results if tissue expansion is completed alongside treatment with radiation.⁶¹ Patient education about risks and alternatives is critical and there must be an understanding of these different options/strategies before any reconstruction is initiated in patients receiving radiation for breast cancer treatment.

The hypoplastic breast

Tissue expansion has played an important role in the reconstruction of both acquired and congenital breast

hypoplasia. Management of the deformity depends on the degree of breast asymmetry, the nature of the deformity, the quality of the chest wall soft tissue, and the age of the patient at presentation.

Unilateral hypoplasia varies from a smaller, well-formed breast to total absence of the breast. These cases further have variable hypoplasia or aplasia of the nipple and areola. If a hypoplastic nipple–areola complex is present, it will usually lie in a cephalad position relative to that of the contralateral breast.

The degree of breast hypoplasia is determined and characterized as minor hypoplasia with a normal nipple–areola complex, moderate to severe hypoplasia, or total breast aplasia. The nipple–areola complex is characterized separately as normal, hypoplastic, displaced, or aplastic. Mild breast hypoplasias may be corrected with simple placement of a breast implant, but more severe hypoplasias and aplasias with nipple–areola displacement are best treated with initial placement of a tissue expander. If pre-surgical examination reveals that the pectoralis muscle is absent, the deformity is probably associated with Poland syndrome (see below).

A tissue expander is placed through either an inframammary or axillary incision into the subpectoral space. The surgeon may choose from many expanders: these include smooth and textured implants, implants with integrated valves, and expanders with distal ports. The prosthesis is initially expanded at 2-week intervals. As the expander is inflated and the overlying skin relaxes, the cephalad-displaced nipple–areola complex will descend. The more slowly the expander is inflated, the better the nipple–areola will descend. A slow expansion also minimizes development of striae. The expander is ultimately overinflated to a volume that is at least 40% larger than the desired volume of the permanent implant. The expander is left in place for several months after the final inflation to allow development of additional ptosis.

The permanent implant is introduced at a second procedure. An incision is made through the original incision that was made to place the expander. The expander is removed, and a capsulectomy is carried out, if needed. If capsulectomy is not needed, the inferior portion of the capsule may be tacked to the rib periosteum to delineate the inframammary fold better. A permanent implant is selected to achieve symmetry with the contralateral side.

Reconstruction with a permanent expander prosthesis is also possible. This prosthesis is inflated to a size several hundred milliliters larger than the desired final volume. The expander prosthesis is allowed to remain overinflated for several months. In the office, saline is then withdrawn to achieve symmetry with the contralateral breast. When desired, the port with its attached tubing is removed through an incision made over the distal port.

The tuberous breast

Expansion is a useful technique in the correction of the hypoplastic tuberous breast. Through an inframammary or periareolar approach, the tuberous breast is lifted off the underlying pectoralis fascia. Radial cuts are made through the breast tissue to expand the base of the breast, and a tissue expander is introduced in the submammary plane. Inflation and expansion are achieved as previously discussed. Once adequate expansion has been achieved, the expander is removed and replaced with the permanent prosthesis. Alternatively, a permanent expander device is used and overinflated by several hundred milliliters. Several months after completion of the inflation, fluid is removed to achieve symmetry with the contralateral side, and the port and attached tubing are removed.

The immature breast

The use of tissue expanders has been beneficial in the management of young adolescents presenting with breast asymmetry.⁶² Adolescence is a critical time that is characterized by intense social pressures and self-awareness of a developing physique, so failure to address the problem of breast asymmetry can result in psychological problems. These patients do not need full maturity for reconstruction.

A subpectoral muscle plane is elevated through a small axillary incision. An expander with an integrated valve or distal port is placed in the subpectoral plane beneath the hypoplastic breast. If a distal-port prosthesis is used, the inflation reservoir is placed in the lateral thoracic wall or in the upper abdomen below the inframammary fold. The prosthesis is then inflated at intervals appropriate to maintain symmetry with the developing breast on the contralateral side. The slow expansion will cause the areola to enlarge, and the nipple–areola complex will progressively be displaced caudally to a more normal position. The adolescent can continue with normal activities, participation in sports, and other physical endeavors.

Once development of the contralateral breast has stabilized, usually between 18 and 19 years of age, the expander is removed. Definitive reconstruction is achieved as previously described for correction of the mature breast.

Correction of Poland syndrome

Poland syndrome involves not only abnormal development of the breast but also thoracic wall deformities, deformities of the upper extremity, and vertebral anomalies. Poland syndrome exhibits a uniform absence of the sternal head of the pectoralis major muscle. Further structural problems may be seen and include abnormalities in the anterior ribs and costal cartilages and deficiencies of the muscles of the scapular area, including the latissimus dorsi. Other findings include deficiency of subcutaneous tissue, hypoplasia, aplasia, or

malposition of the nipple–areola complex, and deficiency of breast tissue.

A mild deformity characterized by breast hypoplasia or aplasia is corrected with the initial placement of a tissue expander through a transaxillary approach. A 700-mL or larger expander may be required to achieve full expansion over a 3–4-month period. Then the tissue expander is removed and a permanent breast implant is placed. Ideally, if there is an inadequate anterior axillary fold and adequate latissimus dorsi muscle, it may be transposed to cover the breast prosthesis. Its insertion is taken down and transposed anteriorly on the humerus to form an anterior, axillary fold. Alternatively, the tissue expander can be placed at an initial operation and covered immediately with a latissimus dorsi muscle transposition. Once expansion has been completed, the expander is removed and the permanent breast implant introduced.

More severe cases of Poland syndrome that are characterized by contour depression of the ribs will require either an osteotomy and repositioning of the ribs or the use of a custom, solid, silastic implant. The anterior axillary fold is reconstructed by transposition of the insertion of the latissimus dorsi muscle over the custom silastic implant. The breast contour is reconstructed with tissue expansion and the subsequent use of a permanent breast implant.

In the immature girl with Poland syndrome, expanders are placed at the onset of contralateral breast development through a small incision in the axilla. To maintain aesthetically pleasing symmetry, the implant is gradually inflated until development of the contralateral breast has stabilized. In the final months of treatment, the expander is overinflated by 200–300 mL and then replaced with the permanent implant. If a latissimus dorsi muscle is available, it is transposed at this time to cover the breast prosthesis (Fig. 25.15).⁶²

Expansion of the trunk

The trunk and abdomen are well suited to tissue expansion in individuals of all ages. Because of the large adjoining surface area from which tissue can be recruited, large prostheses can be placed and flaps quickly expanded (Fig. 25.16). Expansion of the trunk with large prostheses may produce significant deformity and discomfort. Expansions of the back and buttocks are particularly difficult for the patient because of their interference with activities of daily living. Fortunately, using multiple prostheses in such areas produces sufficient tissue for completion of the reconstruction, minimizes distortion, and allows rapidly expedited expansion.

Large prostheses can be either placed above the fascia or incorporated between fascia and muscle planes in the abdomen or on the back. Incorporation of any of the latissimus dorsi, pectoralis major, or rectus muscles allows development of an expanded myocutaneous flap. Prostheses placed between layers of the abdominal wall have been used to develop large flaps for abdominal wall reconstruction (Fig. 25.17).⁶³

Large deformities, such as burns, giant hairy nevi, and other congenital anomalies, may require multiple serial expansions. In such cases as these, the expanders are inflated maximally and the flaps are advanced. The prostheses are left in place and re-expansion is carried out in the subsequent weeks. In the abdomen, two or three serial expansions are usually well tolerated, even in children.

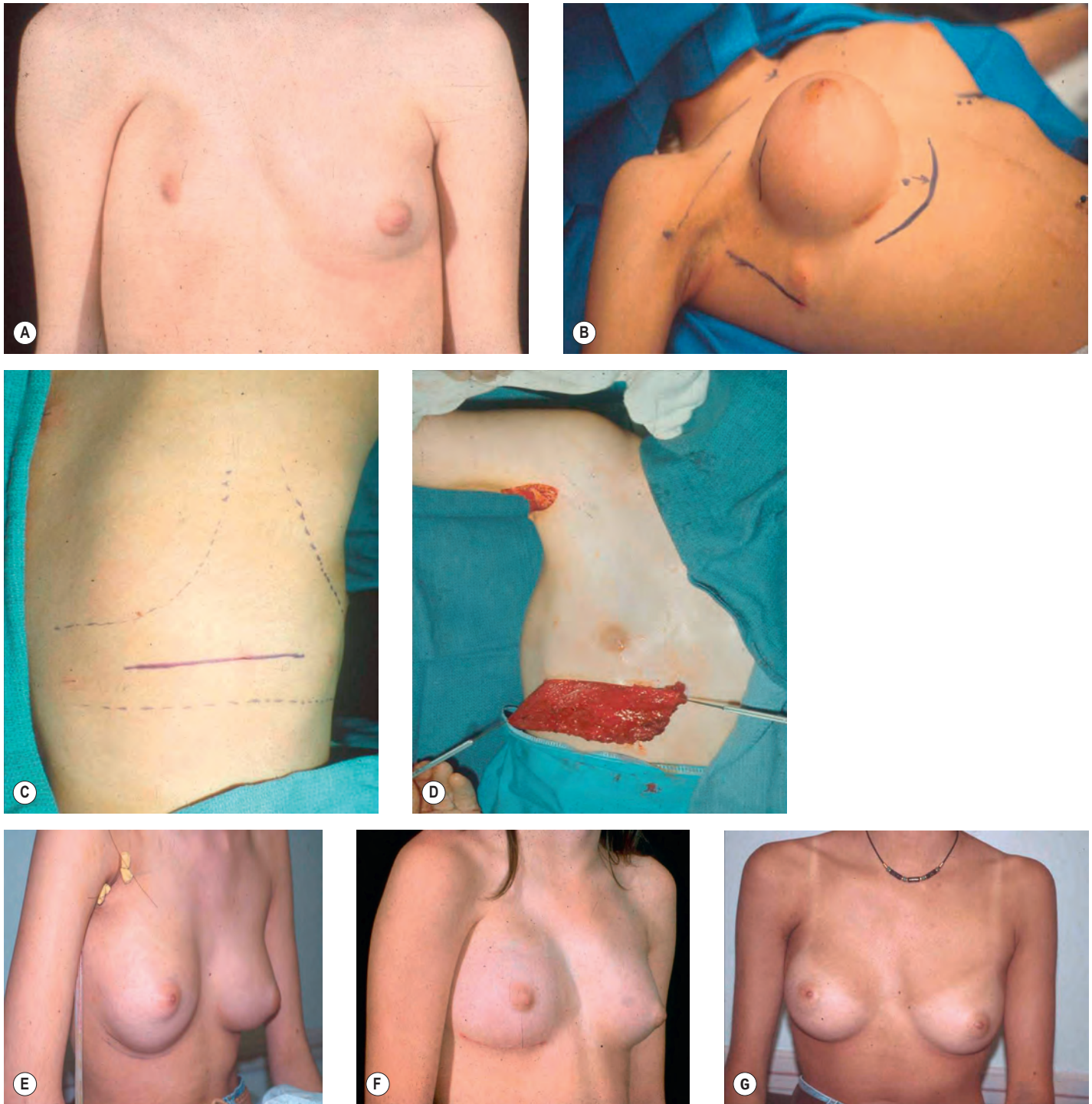


Fig. 25.15 (A) This 17-year-old patient presented with severe right breast hypoplasia with nipple hypoplasia and superior malposition of the right nipple as a feature of her Poland syndrome. (B) She underwent the subcutaneous placement of a tissue expander beneath the skin and soft tissues of the right breast to expand the soft-tissue envelope and increase the distance from the clavicle to the nipple. A latissimus dorsi muscle flap was harvested using two small incisions on the back and single incisions in the axilla and inframammary region of the breast. (C, D) The muscle was transposed to the chest through a high axillary tunnel and placed beneath the expanded soft-tissue envelope and anchored to the parasternal area and inferior aspect of the expanded breast envelope. (E) An implant was placed beneath the muscle to provide the necessary volume to the breast reconstruction, producing an immediate and (F) long-term improvement of the breast appearance at 3-year postoperative follow-up. (G) This produced an excellent change in the breast appearance at 3-year follow-up after surgery. (This case courtesy of Julian J. Pribaz MD. Reproduced from Hall Findlay E, Evans G. *Aesthetic and Reconstructive Surgery of Breast*. Edinburgh: Elsevier Saunders, 2010. © Elsevier 2010.)



Fig. 25.16 (A) Separation of ischiopagus twins was aided by first expanding both the anterior and posterior trunk skin. (B) At a second procedure, the hemipelvis of each side was brought together with the opposite side by closing the pelvic ring over expanded soft tissue. Soft tissue was adequate to achieve total closure in both infants. The children have now survived over 10 years since separation and are doing well.

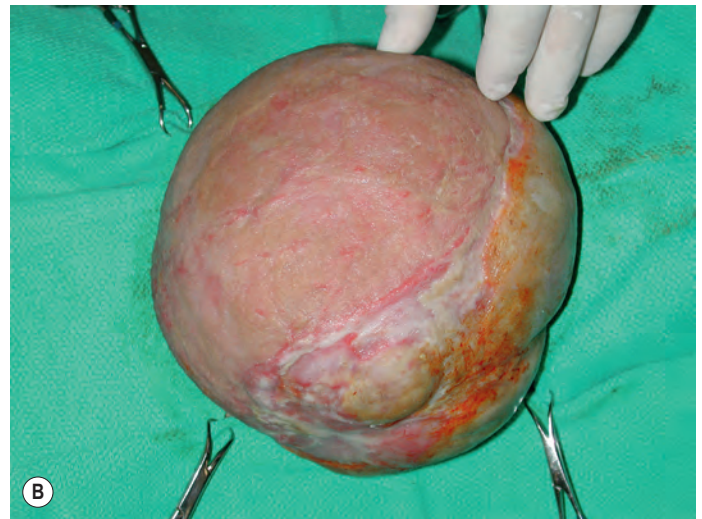


Fig. 25.17 (A) A ruptured omphalocele including the liver had failed reconstruction on two attempts. (B) The abdominal contents were enclosed in Alloderm™ and a vacuum-assisted closure dressing placed over it to colonize it with granulation tissue. When adequate granulation tissue had been developed, a cultured split-thickness skin graft was placed over the entire defect. (C) At 4 years of age, expanders were placed beneath and lateral to the rectus muscle to generate adequate skin and muscles for abdominal closure. (D) The viscera was reduced to the abdominal cavity and the rectus muscles were brought together in the midline to create a stable abdominal wall. The patient has remained stable for 7 years without further surgery.

Expansion in the extremities

Skin and soft tissues of the extremities tolerate tissue expansion well,⁶⁴ so tissue defects resulting from congenital abnormalities, tumor, or trauma may be corrected. The capsule that develops adjacent to the expander has a resilient surface that can be transposed over joints and tendons to decrease adhesions.

The use of multiple expanders in the extremity has the advantages of less distortion, less compromise of everyday life activity, and more rapid development of tissue. Standard rectangular and round prostheses usually suffice and they are best placed axially to the defect. Functional impairment, even when the prostheses are placed directly over vessels and nerves, is unusual. Occasional transitory neuropraxias have been described in the lower extremity but are uncommon in the upper extremity. If such discomfort or neuropraxia develops, the prostheses should be deflated and then re-inflated at a much slower rate.

In areas such as the hand or foot, custom implants may be fabricated. The dorsum of the hand or foot lends itself well to expansion, whereas the palm and plantar areas are particularly painful during, and resistant to, expansion. Expanded full-thickness grafts harvested from the abdomen are extremely versatile in reconstruction of the foot and hand. These grafts are stable and can be harvested as a single graft. Reasonable protective sensation returns to these grafts over time.

The upper leg is easily expanded because of the thickness of skin and its underlying subcutaneous tissue: one large expander or multiple smaller expanders may be used. Complications are infrequent. However, below the knee, inflation carries major risks. Clean, isolated defects, such as those that follow local tumor excisions, are more amenable to expansion than sites where large areas of previously traumatized skin surround the defect. Multiple small expanders are recommended to minimize the risks of implant loss. If cellulitis or tissue compromise occurs during expansion, the prosthesis should be deflated or removed.

Lower leg expansion after crush injuries carries particularly high risk. Individuals who have suffered major crush or degloving trauma to the extremity are better treated with function-restoring microvascular and myocutaneous flaps than with attempts at excessive aesthetic reconstructions using tissue expansion.

Wound management with negative pressure therapy

Negative pressure wound therapy (NPWT) uses the principle of applying mechanical force to cells surrounding a wound to stimulate the induction of new tissue development that will subsequently aid in closure of that wound.³

Historical perspective

The use of vacuum forces on wounds was described in 1995 by Fleischmann who employed the technique of placing suction drains wrapped in porous polyvinyl alcohol foam into wounds.⁶⁸ These wounds were sealed with polyurethane drapes and then the drains were attached to a suction apparatus at 600 mmHg. In 1997, Drs. Argenta and Morykwas at Wake Forest University presented their experience with vacuum-assisted closure (VAC) devices.³ They presented the use of the VAC in 175 chronic wounds, 94 subacute wounds,

and 31 acute wounds over a nine-year period in conjunction with their animal study experience over the same period. Clinically, the application of negative pressure causes the dressing sponge to collapse towards its center producing deformation and traction forces applied to the wound perimeter pulling the wound edges together which progressively make the wound smaller. In addition, NPWT removes wound edema, appears to increase circulation and decrease bacterial counts, and significantly increases the rate of granulation tissue formation.⁶⁹

Cellular and molecular basis of NPWT

The mechanical effects of NPWT on wounded tissues and their subsequent cellular and molecular effects are actively being studied. At a cellular level, NPWT alters wound bed gene expression with resultant changes in cytokine/chemokine/growth factor expression and matrix metalloproteinase (MMP) expression. In human and animal models, increases in anti-inflammatory cytokines (IL-10) and pro-angiogenic growth factors (VEGF, FGF, PDGF) have been demonstrated with the use of NPWT. The above, in conjunction with reduction in MMP expression, indicates that NPWT may promote healing by modulation of cytokines to an anti-inflammatory profile and alteration in mechanoreceptor- and chemoreceptor-mediated signaling to culminate in angiogenesis and extracellular matrix remodeling for the deposition of granulation tissue.¹⁸

The vacuum-assisted closure (VAC) device

The basic VAC system consists of sponge material composed of reticulated polyurethane or polyvinyl alcohol (white foam) cut to fit the wound, an occlusive drape, suction tubing, and adjustable vacuum pump with a collection canister. Since its introduction, many technologic improvements have been made, making this technique more user-friendly. Advances include smaller device and battery, the ability to modulate pressures applied to the wound, improved fluid management capabilities, the availability of different types of foams to be tailored to wound characteristics, and the addition of safety precautions/leak alerts to the device.⁶⁵

Patient selection

Vacuum-assisted closure devices were initially designed for the management of chronic wounds such as diabetic ulcers, venous stasis ulcers, and pressure ulcers in order to simplify wound care in this patient population or bridge wounds until factors preventing definitive wound reconstruction could be resolved or improved. Today, this technique can be safely applied to all patient populations and in a wide range of acute or traumatic soft tissue injuries including wounds with compromised soft tissues, contaminated wounds, hematomas, and gunshot wounds.

Despite the myriad of clinical scenarios where a VAC can be utilized, there are specific contraindications to its use. It should not be used when hemostasis is inadequate as the negative pressure may continue to remove blood from an actively bleeding or oozing wound. NPWT application should be avoided if necrotic or sloughing tissue is present. In general, prior to application of NPWT, aggressive surgical debridement of all nonviable tissue and any foreign body is performed, appropriate coverage of critical structures is completed (major

vessels, viscera, nerves) utilizing local muscle or soft tissues, and then NPWT initiated.

NPWT technique

Negative pressure wound therapy requires placement of a sponge material on or into the wound. An occlusive drape is then placed over the sponge and onto the surrounding skin. An opening is made in the occlusive drape, and the suction tubing is fixed to the exposed sponge with an occlusive seal. The suction tube is attached to the collection canister which is attached to the adjustable vacuum pump. The vacuum pump can be used as continuous or intermittent vacuum using pressures of 75 to 125 mmHg when using polyurethane foam and as higher continuous pressures of 125 to 175 mmHg when using polyvinyl alcohol foam. VAC foam dressing can safely be changed at 2 to 3 day intervals. At the time of foam change, other traditional wound healing modalities, such as pulse lavage, can be used. Silver-impregnated foam sponge has been introduced to provide a bactericidal sponge in patient with colonized wounds. This technique is continued until the goal of wound closure is achieved or the wound undergoes elective reconstruction with standard techniques.

Special considerations

Decompressive fasciotomy wounds

NPWT may be employed in the management of wounds following decompressive fasciotomy. With negative pressure, the edematous muscle and soft tissues are decompressed rapidly over a period of 2–3 days. The interval between fasciotomy and wound closure may be lessened with this technique and may increase the likelihood of primary closure rather than skin grafting, which has been the traditional method of management of fasciotomy wounds treated with daily saline dressing changes.

Skin grafting/dermal substitutes

Vacuum-assisted closure provides an alternative method with which to bolster a skin graft or dermal substitute.⁷⁰ The sponge is cut to conform to the wound and, when the air is withdrawn from the sponge, the firm sponge serves as a stent that maintains the graft/ substitute in place during the process of revascularization. Furthermore, the negative pressure therapy aids in neovascularization providing a better wound bed for full thickness skin grafts, dermal substitutes,⁷¹ and grafts on the diploic layer of bone with little granulation.

Acute burns

Morykwas showed in a swine model that NPWT decreases burn wound progression.⁷² This is likely due to the removal of edema fluid allowing for improved blood flow into the burn wound environment. This in turn minimizes tissues in the zone of stasis progressing to the zone of coagulation with subsequent tissue necrosis. When applied to hand burns, NPWT results in more rapid reduction of hand edema allowing improved physical therapy and hand mobility.

Incisional VAC application

The collapsed VAC sponge does not traumatize a fresh wound closure or a fresh flap. During the first 24 hours after wound

closure the wound is not yet sealed, and the VAC is beneficial in drawing serous fluid from between the sutures of the closure. It may be applied over a fresh flap and does not result in any compromise to the underlying flap. Recently, application of NPWT to incision closure has been more frequently employed. There is a growing body of literature that demonstrates reduced incidence of wound healing complications with the use of incisional wound VAC application for a period of 3–5 days.^{73,74}

Postoperative care

In general, expanders should be partially inflated immediately after wound closure. This allows closure of “dead space” to minimize seroma and hematoma formation. It also smooths out the implant wall to minimize risk of fold extrusion. Enough saline is placed to fill the entire dissection space without placing undue tension on the suture line.

Serial inflation usually starts 1–2 weeks after initial placement, although inflation schedules can be individualized to the specific case and the tolerance of the patient. Inflation reservoirs seal best when a 23-gauge or smaller needle is used. A 23-gauge butterfly intravenous needle is especially useful; it allows the patient to move slightly without dislocating the needle. Frequent small-volume inflations are better tolerated and are physiologically more suited to the development of adequate overlying tissue than are large infrequent inflations.

For practical purposes, most prostheses are inflated at weekly intervals. On occasion, accelerated inflation schedules may be followed.⁴¹ In children who have devices with external ports, small-volume inflation at 2–3-day intervals is well tolerated. Individual inflations proceed until the patient experiences discomfort or blanching of the overlying skin. In hypoesthetic areas, objective changes in flap vascularity must be evaluated with particular care. Although a variety of devices such as pressure transducers and oxygen tension monitors are available to help determine proper inflation, an objective evaluation of the patient's response is usually a reliable indicator of appropriate inflation. Serial inflations proceed until an adequate amount of soft tissue has been generated to accomplish the specific surgical goal.

Specific to breast tissue expansion, the frequent visits required to inflate the expansion device fully create some inconvenience for patients, who are seen every 7–14 days. This process usually continues for 2–3 months, depending on the desired final size of the implant. Overinflation is helpful when permanent breast implants are to be placed. Inflation of breast expanders by 20% over capacity is commonly performed so that after the permanent implant is placed, some ptosis of the breast can be developed.

Complications and their management

Initial attempts at tissue expansion were associated with a high rate of complication which included, but were not limited to, implant failure due to either puncture during inflation or mechanical problems. As more experience accumulated, however, the incidence of complications dramatically decreased. Complication rates are directly proportional to the number of expansion procedures performed and the experience of the individual surgeon.⁶⁶ Most complications incurred

during tissue expansion are relatively minor and do not interfere with completion of multistage procedures.

Implant failure

Despite design improvements, the use of an excessively large needle or the inadvertent puncture of the implant can lead to implant deflation. To maximize sealing of the valve, the implant reservoir should be entered at a 90° angle. If there is any question about the location of the inflation reservoir, radiologic or sonographic techniques may be helpful.

Infection

As with the placement of any prosthetic device in the human body, infection is possible. The introduction of bacteria to the wound in the perioperative period is the most common cause of early infection. The area to be reconstructed should be stable, and there should be no open wounds at the time that the procedure is undertaken. Areas susceptible to lymphedema, such as traumatized lower extremities, carry a significantly higher rate of infection. An area of copious lymphatic drainage, such as the neck or the groin, also tends to accumulate lymphatic fluid around a prosthesis and is more susceptible to infection. These areas should be drained with suction drains until all excess drainage stops. Antibiotics are given as long as the drain remains in place.

Late infections are usually caused by iatrogenic introduction of bacteria during the course of inflation. The inflation procedure should be performed under sterile conditions in the office. Povidone-iodine (Betadine®) is used to prepare the injection site. Externalized distal ports carry a high colonization rate, but the resultant contamination produces little complication. Many infections can be difficult to detect and can be tolerated well by the patient.⁶⁷

Some erythema may occur over all expansion prostheses; however, pain, warmth, and systemic symptoms such as fever and chills suggest clinical infection. If the infection occurs in the perioperative period or early course of expansion, the prosthesis should be removed and the wound irrigated. The

procedure is aborted, and a second attempt is made 3 or 4 months after healing. If infection occurs late in the course of expansion, the prosthesis can be removed and the expanded tissue advanced after irrigation of the infected cavity. Permanent implants should not be placed when Gram stain of the expander space reveals bacteria.

Implant exposure

Implant exposure can occur both early in the postoperative period and after a protracted course of expansion. Treatment of the exposed implant depends on the timing of exposure. Exposure early after placement is usually related to inadequate dissection or use of an excessively large prosthesis that abuts on wound closure. If the prosthesis becomes exposed soon after placement, it is best to remove it and re-operate 3–4 months later.

Late exposure is usually related to excessively rapid or overzealous inflation. Rapid expansion is medically necessary only in few instances. Tissue expansion should be carried out judiciously to achieve optimal cosmetic results. If minimal or late exposure occurs during the course of expansion, the procedure can continue with the use of antibiotic creams on the exposed area. In this situation, multiple, rapid fillings are done to generate adequate tissue. Reinforcement of the compromised overlying skin with paper tape is sometimes helpful. Most flaps survive and do well even with some exposure of the implant.

In compromised tissues, such as grossly traumatized lower extremities or irradiated and burned tissues, the use of tissue expansion can more easily result in implant exposure – a cautious approach is warranted.

Compromise and loss of flap tissue

Tissue expansion exerts changes on living tissue similar to those seen in the phenomenon of conventional flap delay.²⁹ Expanded flaps are almost universally more robust than non-expanded flaps. To ensure vascularity, one should attempt to maintain a major axial vessel in the expanded tissue.



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Principles of radiation

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SYNOPSIS

- Radiation therapy (RT) can be used as a primary or adjuvant treatment for many cancers.
- The unit of dose measurement is the gray (Gy).
- Side effects are characterized as acute and late toxicities.
- Acute toxicities are temporary and reversible.
- Late toxicities are permanent.
- The primary mechanism of action of radiation is through breakage of DNA strands.
- Treatment planning is achieved through use of three-dimensional computed tomography (CT) planning.
- Delivery of radiation can be very precise with the use of intensity-modulated radiation therapy (IMRT) as well as with image-guided radiation therapy (IGRT).



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Introduction

Radiation therapy (RT) requires an understanding of physics. A multidisciplinary team, including radiation oncologists, physicists, dosimetrists, and radiotherapists, is required for the delivery of radiation. Delivery of radiation can be achieved using different modalities, including kilovoltage, orthovoltage, megavoltage, electrons, protons, and brachytherapy.

RT utilizes ionizing radiation to treat malignant tumors and some benign disorders. Nearly two-thirds of cancer patients receive RT as part or all of their treatment. Radiation oncology is the discipline of medicine that addresses the causes, prevention, and treatment of human cancer with special emphasis on the role of ionizing radiation.⁴ Radiation oncologists work in a multiprofessional team with radiation therapists, nursing, dosimetry, and medical physics, along with dietitians, social workers, and counselors. Radiation therapists are the technologists who deliver the RT; they

spend not only considerable time on the technical components of treatment (treatment delivery, quality assurance, and verification), but also interact with and support cancer patients throughout the duration of their therapy. Radiation oncologists work with surgical and medical oncologists, diagnostic radiologists and pathologists, and are essential participants at tumor board for multidisciplinary decision-making. Outside the immediate team, it is rare for other physicians to know much about the technology, process, rationale, and issues around RT, and even less about the risks and causes of toxicity. This chapter is designed as a primer, or virtual elective in the topic, and aims to improve communication and understanding between plastic surgeons and radiation oncologists so that they can better appreciate some of the common issues faced when caring for cancer patients. This chapter starts with a brief description of the basics of radiation technology, modalities, medical physics, and radiobiology. It then outlines practical applications, with a description of RT planning and process, and clinical treatment issues for select cancers. The final section describes specific toxicity syndromes.

Radiation technology

RT has consistently relied on technology. Although much of the equipment that has been the mainstay of RT is being replaced by newer technology, some of it remains in effective and efficient use. For example, kilovoltage therapy can be effectively used for very superficial treatments. It delivers 100% of the prescribed dose at the skin, has rapid fall-off below the skin, and a tight penumbra (edge of the beam). In the 50–150-kV range, penetration provides useful coverage only to a depth of 5 mm; orthovoltage therapy (150–500 kV) provides better penetration, but is not capable of treating much more than 3 cm below the skin. With kV energies, skin dose becomes the rate-limiting step. At the orthovoltage range of energy, interaction between radiation and matter is strongly dependent on the atomic number (Z) of the attenuating material. For the photoelectric effect, high Z tissue, such as bone, attenuates more

Historical perspective

In November 1895, Wilhelm Conrad von Roentgen discovered a new type of ray that was generated from a stream of electrons in a cathode gas discharge tube and had the ability to pass through tissues with different degrees of penetration. Because the composition of the rays was unknown, they were called X-rays. His subsequent presentation to the Würzburg Society on the ability of his rays to generate an image of structures inside the body gave birth to diagnostic radiology. The following year, in France, Henri Becquerel discovered that fluorescent materials made of uranium also emitted constant radiation.¹ Marie and Pierre Curie used ionization to measure becquerel rays and quantify radiation intensity against uranium. Marie Curie first used the word “radioactivity” in 1898. The couple isolated two new radioactive elements from pitchblende, polonium, named for Marie’s native Poland, and radium, Latin for ray. Today, these pioneers’ names are in constant use as measures of radioactivity.²

The earliest oncologic brachytherapy procedure was in 1902, when a radium applicator was used to treat a tumor of the palate and pharynx. Within a few years, there were clinical studies of effectiveness, and radium tubes were inserted directly into tumors, and by the 1920s, radium had become the standard of care in oncology,³ as well as the treatment for many benign conditions. The use of Roentgen’s rays to palli-

ate advanced cancer was first described in 1903,⁴ and this was the forerunner of external-beam radiation treatment.

Until the 1950s, most radiation machines were very similar to diagnostic radiology ones, and generated X-rays at potentials of up to 300 kV. Superficial therapy (50–150 kV) could treat to a depth of 5 mm, and thus was useful for superficial skin cancers. Orthovoltage (or deep) therapy (150–500 kV) provided greater penetration, but was not capable of treating much more than 3 cm below the skin, with 100% of the dose at the skin. At this range of energy, interaction between radiation and matter is strongly dependent on the atomic number (Z) of the attenuating material – in other words, in this process, known as the photoelectric effect, tissue such as bone, which has a high Z, attenuates more radiation; fat and soft tissue (lower Z) attenuate less; and air (for example, in the lungs) hardly at all, thus producing the contrast necessary for diagnostic imaging. Unfortunately, this higher absorbed dose in bone resulted in many more problems from osteoradionecrosis (ORN).

The development in Canada of the cobalt-60 unit in 1951 introduced the new era of megavoltage (MV) radiotherapy to the world, allowing greater penetration of tissue and, with maximal dose not achieved until a depth of 0.5 cm, resulting in better skin-sparing and improved dose homogeneity. Since then, computer-controlled megavoltage linear accelerators have been developed, providing increasing penetration and skin-sparing, and a rapid accumulation of technologies to verify, deliver, and record increasingly precise RT.

radiation than lower Z tissue, such as fat and lungs, producing the contrast necessary for diagnostic imaging. Unfortunately, this higher absorbed dose in bone resulted in many more problems from osteoradionecrosis (ORN).

Megavoltage radiotherapy allows even greater penetration of tissue, resulting in better skin-sparing and improved dose homogeneity. It is not influenced by the atomic number of the absorbing medium, as Compton scattering is predominant in this energy range.

Cobalt units deliver MV radiation, and have a ^{60}Co source that generates gamma (γ) rays with average megavoltage energy of 1.25 MV. ^{60}Co has a half-life of 5.26 years, and as a result of this decay and subsequent drop in output, the source needs to be replaced every few years. Maximum dose (D_{max}) is not achieved until 0.5 cm beyond the surface of the skin and the intrinsic scatter of the beam and ionized particles means that the penumbra, or dose fall-off at the edge of a beam, is not very tight. Despite this, cobalt is still a prevalent and important external-beam radiotherapy modality, as it still provides an excellent low-maintenance, reliable, safe, and effective alternative in many low- and middle-income countries.

Photons are the most commonly used RT modality. They are generated by a linear accelerator, or linac, which uses high-frequency electromagnetic waves to accelerate electrons to a very high energy through an accelerator tube and beam transport system. When the accelerated electrons hit a high Z target at the end of this, they produce megavoltage X-ray beams that have sharper edges and can penetrate deep tissue. Typical photon energies produced by linacs are 4, 6, 10, and 18 MV that result in increasing maximum depth doses.

Particle therapy

Electrons are the most commonly used particle therapy. They are also generated by linacs by removal of the target in the beam's path for production of electron beams. Most linacs can produce a range of electron energies from 4 to 17 MeV. They deposit their energy superficially, sparing structures deeper in the body, with fairly steep dose distribution curves. Electrons produce more side scatter than photons and have wider penumbras. They are typically used to treat skin cancers, "boosts" to breast tumor cavities, and for intraoperative radiotherapy. They are also used to spare sensitive organs that may otherwise reach maximum tolerance, for example, protecting the spinal cord when treating posterior neck nodes.

Many new proton facilities are opening nationwide; they are expensive and cumbersome to construct and maintain, requiring a cyclotron or a synchrotron to accelerate protons, which have a mass nearly 2000 times that of an electron. Protons have similar biologic activity as photons; their advantage is that they have a unique shape to their dose distribution, with low steady-dose deposition until near the end of their clearly defined range when the dose peaks then falls sharply to nearly zero. This is the Bragg peak phenomenon, which allows very precise dose distribution, protection of critical structures, and dose intensification. By combining different beam energies, a spread-out Bragg peak (SOBP) is created which is able to encompass the target in its entirety to the prescribed dose. Protons are ideal for treating structures in the base of skull, such as the clivus, especially for chordomas, where the necessary dose is far above the tolerance of the sensitive optic chiasm

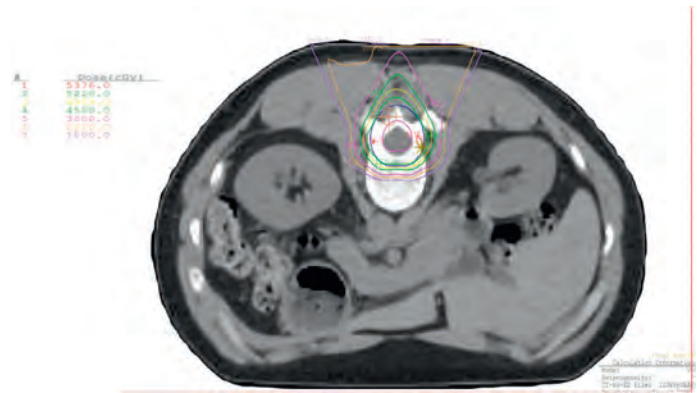


Fig. 26.1 Axial proton treatment plan for a spinal myxopapillary ependymoma with sparing of the bone marrow and anterior-lying organs. (Courtesy, Jason K. Rockhill MD PhD.)

and other sensitive structures in that region, and would otherwise cause severe toxicity, or for spinal cord tumors, such as ependymoma (Fig. 26.1). Another indication for protons is to deliver craniospinal irradiation for pediatric cancers such as medulloblastoma, because the proton dose distribution significantly reduces the exit dose to anterior structures (kidneys, bowel, lungs) when compared to conventional photon therapy (Fig. 26.2). Proton beam radiotherapy is useful for reirradiation as it often can reduce dose to critical structures that have



Fig. 26.2 Comparison of photon and proton craniospinal radiation treatment plans for pediatric medulloblastoma. Both techniques use a single posterior beam, but the proton plan has significantly less exit dose. (Courtesy, Ralph Ermoian MD.)

already been exposed to prior radiation. Proton beam radiotherapy is also utilized for the treatment of prostate cancer and shown to have high efficacy with minimal bowel and bladder toxicity,⁵ but long-term data are needed to compare late toxicity rates with photon beam RT. However, changes in tissue heterogeneity can affect where the particle stops and the position of the Bragg peak, leading to some uncertainty in dosing. Currently, there are several ongoing randomized trials that are evaluating the role of protons versus photons in respect to survival, toxicity, and quality of life outcomes. Some currently accruing trials include RTOG 1308 for inoperable non-small cell lung cancer and NRG-BN001 for glioblastoma.

Neutron RT, first used for cancer therapy in the 1930s, offers the advantage of high linear energy transfer, a property that allows the delivery of 20–100 times more energy along their path than photons, thus being biologically more effective in treating radioresistant tumors such as sarcomas and salivary gland tumors.¹ Their use requires a careful balance of risk and benefit as they can lead to more severe late toxicities.⁶

Carbon, neon, and heavier ions hold promise as they combine the radiobiological advantages of neutrons with the dose distribution and Bragg peak of protons, but are only available in select centers.

Brachytherapy

Brachytherapy, meaning “short distance” in Greek, is a method of delivering radiation treatment near or within a target using radioactive sealed sources. There are three main ways of delivering this type of radiation: (1) an applicator can be used to deliver dose to the surface of a thin tumor, for example, an eye plaque used to treat ocular melanoma; (2) intracavitary – inserting the sealed source into the cavity of an organ, e.g., in the treatment of cervical cancer, a combination (tandem) apparatus is used consisting of a cylindrical rod inserted into the cervical os and through the cervical canal into the uterus, with two ovoids placed in the lateral fornices; and (3) interstitial, when the source is either implanted directly into the tumor or postoperative bed, for example, for postoperative treatment of sarcoma, or when radioactive gold seeds are implanted directly into an organ, e.g., in the treatment of early-stage prostate cancer. Brachytherapy is often used in conjunction with external beam, usually to increase the total dose to a smaller volume at the site of greatest risk of recurrence, for example, in the postoperative management of cervical cancer.

Following the work done by Marie Curie and others, radium needles were initially used, until the importance of radioprotection was realized. In the modern era, artificially produced radionuclides are used, most commonly those derived from cesium (^{137}Cs), iridium (^{192}Ir), iodine (^{131}I), palladium (^{103}Pd), and gold (^{198}Au). The activity of these radionuclides is still calculated relative to that of radium. To protect health professionals and the patient, the process of using high-energy sources, such as ^{137}Cs and ^{192}Ir , has evolved considerably, most notably with the use of after-loading. Empty cylinders (for intracavity) or catheters and trocars (for interstitial brachytherapy) are inserted, and loaded with inert metal “dummy” sources that are visualized on radiologic imaging; this is done to verify the position and calculate the dose distribution. The patient is treated in a shielded room, either as an inpatient over several days, or in an outpatient brachytherapy suite, for shorter high dose rate treatments.

The radioactive sources are housed in a shielded safe in a remote-controlled after-loading unit, which looks very much like a small heating furnace. After a final verification of positioning, the applicator, catheters, cylinders, or trocars are connected with tubes to the after-loading unit. After all personnel have left the room, the active sources, which look like small beads, are remotely loaded through a pressurized system. The unit is programmed to control the position of the sources and the duration of the sources in any position to achieve the prescribed dose in a homogeneous fashion over the three-dimensional dose distribution. The unit can be paused, and the active sources retract temporarily into the safe within the after-loading unit, making it possible for personnel to enter the room to provide care.

Low-energy radionuclides such as ^{131}I , ^{103}Pd , and ^{198}Au do not pose the same concerns for radioprotection, and thus are used as permanent implants in the form of seeds, most commonly for prostate cancer.

Physics

An explanation of RT techniques and dosimetry requires a basic understanding of physics. The photons generated by the linac are very high-energy X-rays that do not have any charged particles in them. When a photon beam enters the body, it uses the Compton process to deposit energy. This means that it interacts with tissue by colliding with an atom’s loosely bound outer shell electron (Fig. 26.3). The photon continues along its path, but the electron is knocked off, like a billiard ball, at an angle that depends on the speed and angle with which it was hit. The electron travels (scatters) a distance that is proportional to the energy with which it was hit, meaning that higher photon energies propel electrons more in a forward direction than lower energies can do, before the electron is deposited, and the dose absorbed into the tissues. This triggers downstream free radical interactions, and these can cause DNA single-strand or double-strand breaks, or other injuries, including damage to base pairs and protein cross-links. The chromosomal aberrations that result from double-strand breaks mean that the cancerous cell cannot repair or duplicate at the end of its life cycle, leading to the principal cause of cell death.

If all of these electron energy deposits are added up, then a distribution curve showing absorbed dose and depth can be plotted (Fig. 26.4A) that shows that skin absorbed dose is less than 40%, and 100% or D_{max} occurs some distance into the skin at a depth that is consistent with the energy of the photon beam. The commonest energy used is 6MV, which has a D_{max} of 1.5 cm beyond skin. The dose then falls off at a steady rate

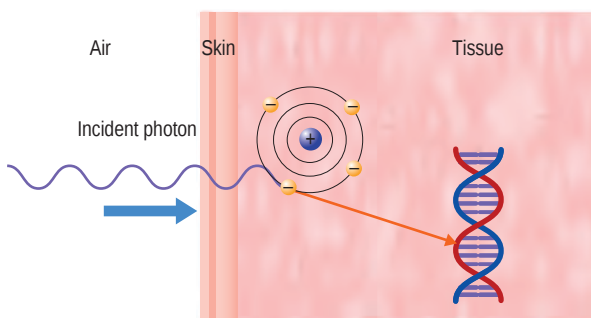


Fig. 26.3 Incident photon knocks an electron off the outer ring and scatters it along a pathway through a distance before the electron energy is absorbed.

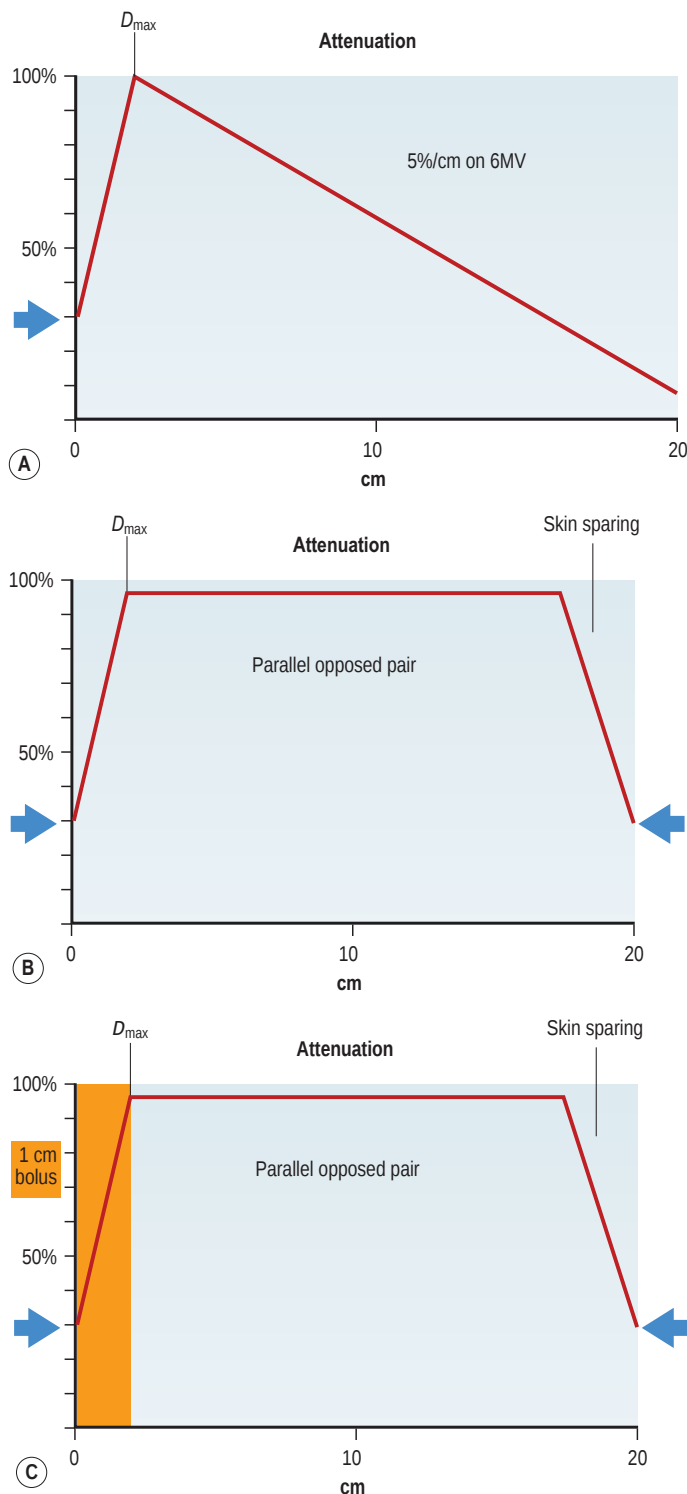


Fig. 26.4 (A) Depth dose distribution for 6 MV photons: only approximately 30% of the dose is absorbed at the skin surface; the maximum dose (100%) is absorbed at a depth of 1.5 cm, and then attenuates by less than 5% per cm. (B) When two beams are opposed, depth doses can be added, resulting in an even distribution across the target volume. (C) If a higher dose is required at the skin surface, a strip of bolus material is placed on the skin.

that is just less than 5%/cm, meaning that 50% of the dose has been deposited approximately 11 cm into the body. If a tumor is situated centrally, this means that there is too much of a gradient of dose across it. To overcome this heterogeneity within the target volume, a second beam can enter the body

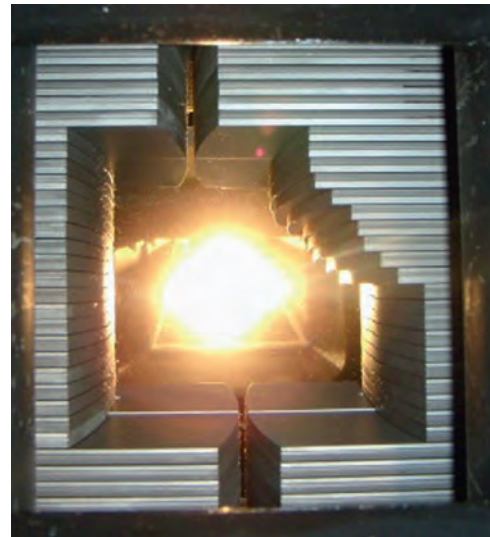


Fig. 26.5 Multileaf collimators (photographed looking into the head of the machine) are used to provide static shielding, or, when programmed dynamically, differential dose absorption for intensity-modulated radiation therapy.

(assuming a diameter of 20 cm) from the opposite side, again depositing its maximal energy at 1.5 cm, then attenuating at <5%/cm. The energy deposits from each side are added, a homogeneous distribution is achieved across the target volume (Fig. 26.4B), and the skin does not receive a therapeutic dose, unless bolus is used (Fig. 26.4C). The addition of right and left lateral beams (four-field box technique) would give an even tighter homogeneous distribution to the target volume, and, since the entrance and exit doses are shared between four beams, further skin dose reduction. This is the basis for using multiple fields, or beams, from different angles, to “focus” (a misleading term, since the beam does not focus on a spot, as light does through a lens) and deposit maximal dose to a target.

In conventional RT, most beams are delivered with uniform intensity across the field. Beam-modifying devices are accessories such as shielding blocks, wedges, and compensators, which are placed in the head of the machine to differentially absorb dose proportionally to the thickness of the device (i.e., more dose is absorbed through thicker regions, and less through thin), to improve dose homogeneity within the target. In modern linacs, blocking is done by a system of multileaf collimators (MLCs), which are narrow strips of metal in the head of the linac that act like miniblocks. Their shape can be programmed for shielding (Fig. 26.5). Three-dimensional conformal therapy uses multiple beams to be shaped in such a way that a significant amount of normal tissue can be excluded.

MLCs can also be programmed to move dynamically in and out of the beam, so that the amount of time in each position is adjusted to allow a variable amount of dose through each leaf, compensates for irregular shapes with great precision, and can control the dose to specified targets within a volume. This is the basis for intensity-modulated radiation therapy (IMRT), which involves identifying doses for individual or multiple target volumes and constraints for normal organs that need to be protected from the effect of radiation, and then using a sophisticated RT planning program that modulates the intensity across multiple individual beams or arcs with dynamic MLC, using an inverse planning system. This allows the creation of a very conformal plan that can even have convex and concave shapes to avoid a critical

structure, for example, avoiding the spinal cord in a way that conventional beams may not achieve (Fig. 26.6). It is also possible to “dose paint” so that different areas receive different doses at the same time, and also to reduce volumes, adapting to reduction in the tumor size. A similar result is obtained with tomotherapy, which uses principles of CT scanning to deliver intensity-modulated beams slice by slice. An advantage of IMRT over this system is that IMRT is delivered on a normal linac rather than a dedicated machine.

Image-guidance is essential for high precision in RT delivery (IGRT). Electronic portal imaging (digital MV or KV

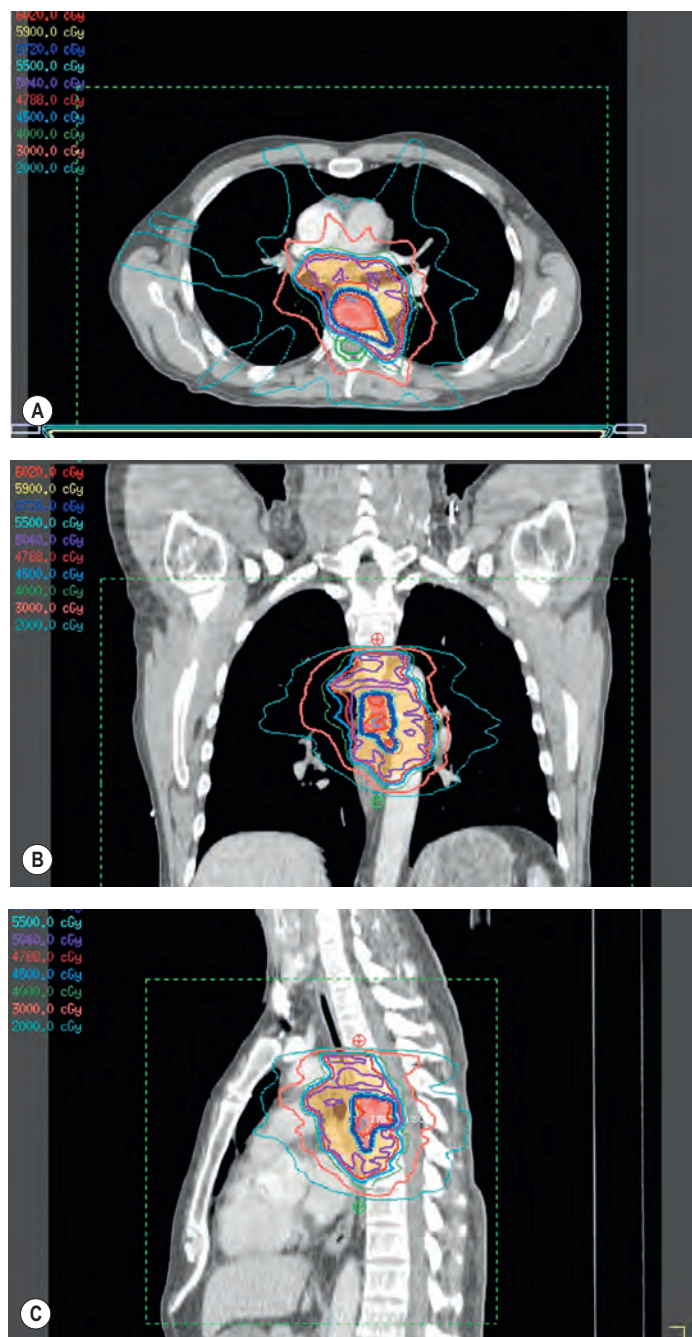


Fig. 26.6 (A) Axial intensity-modulated radiation therapy plan of a sarcoma involving the mediastinum extending into a thoracic vertebral body. The technique allowed a radical dose (66 Gy) to be delivered to the target volume, but constrained the cord dose to a safe dose of 52 Gy. (B,C) Coronal and sagittal distributions.

X-rays taken on the RT machine) can take both orthogonal views of the target, e.g., anterior and lateral beams, and beam's eye view images. The utility of this is enhanced when there are recognizable and stable landmarks, for example, some part of the bony anatomy. However, when the target is mobile, then fiducial markers, such as gold seeds placed in the prostate gland or along the cervical os for brachytherapy, can serve as a surrogate for target location. The cone beam CT (CBCT) uses KV three-dimensional imaging to verify positioning for IGRT on the treatment couch.

Stereotactic techniques like radiosurgery deliver hypofractionated RT to small lesions in structures such as the brain. A linac-based process involves the use of multiple very small beams that cover a small target (2–5 cm) to a large dose of RT, delivering a therapeutically radical equivalent dose in just a few, or even just one, fraction. It has primarily been used on central nervous system tumors, including benign conditions such as arteriovenous malformations or schwannomas, immobilizing the head in a frame. Gamma knife uses a ^{60}Co source with similar principles. With the advent of IGRT, this principle is now applied to stereotactic body RT (SBRT) for sites elsewhere in the body, such as lung, liver, and paraspinal tumors. Large doses, for example 10–18 Gy, are higher depending on tumor size and location, are given 2–3 times weekly over fewer fractions than conventional fractionation to an ablative dose, but with much greater precision, and potentially less toxicity. It is well tolerated even by frail and ill patients.

Intraoperative RT (IORT) is used to treat small areas (3–10 cm) that are at high risk for recurrence immediately after the tumor has been resected, such as a retroperitoneal sarcoma, on the same day. An advantage of IORT is that critical structures, such as bowel, can be physically moved out of the beam's pathway. The radiation oncologist positions electron applicators (also known as cones) into the wound to cover the tissue at risk for microscopic residual disease that has been localized by the surgical oncologist (Fig. 26.7). The



Fig. 26.7 Intraoperative radiotherapy (IORT) delivering a large single fraction of XRT to the operative bed in the retroperitoneum. This photograph shows the cone, or electron applicator (the metal cylinder), after it has been positioned over the target volume. It will now be secured into place, the position verified, the monitor units and dose rate calculated, before personnel leave the room and XRT is delivered. Set-up takes approximately 15–20 minutes, but the treatment is delivered in only 2–3 minutes. (Courtesy, Edward Y Kim MD.)

cone position is stabilized and verified before being aligned with the head of the machine. Medical physicists calculate and verify the delivery. Personnel then leave the room, the beam is switched on, and the dose is delivered in less than 2 minutes. The cone is removed, and the surgeon closes up.

Radiobiology

Radiation injury can be viewed from two perspectives: the radiation effect on tumor cells, and the radiation toxicity on normal cells. The therapeutic ratio is a dose–response relationship between tumor control and normal tissue complications, and helps balance these two perspectives. In an ideal world, the curves representing tumor response and normal tissue complications would be well separated (Fig. 26.8A). Far too often, they are so close together that it is not possible to achieve a high enough dose to eradicate the tumor without causing harmful complications (Fig. 26.8B). Usually in clinical practice there is some degree of compromise, and traditionally, less than 5% risk of normal tissue complications is accepted (Fig. 26.8C), taking into account the specific risks of the situation.

Radiation toxicity is expressed during mitosis of normal cells. Acute toxicity occurs during treatment course or shortly afterwards. It is related to the total dose, the size of the volume irradiated, and radiosensitizing drugs such as chemotherapy. It occurs in cells with a rapid turnover, such as oral mucosa or skin epithelium, where cell division is necessary to maintain function. Even though these cells may be affected within a few days of starting fractionated treatment, their damage does not become manifest for at least 2 weeks as the progenitor stem cells do not have as rapid a turnover. Examples are skin erythema and desquamation, oral mucositis, and esophagitis. Even quite brisk reactions can heal fast once RT is completed (Figs. 26.9 & 26.10). Acute toxicity is reversible and does not predict for permanent damage. The exception is if there is consequential damage, i.e., there is persistent injury due to the destruction of the basement membrane zone with complete depletion of stem cells due to very high dose, and usually an additional factor such as chemotherapy, infection, or trauma. This can be found in chronic ulcers in the skin, bladder, or gastrointestinal tract. Delayed acute toxicity occurs 6 weeks to 6 months after the completion of treatment; it is also reversible. As with acute toxicity, it is dose-, volume-, and drug-related. Examples are radiation pneumonitis and Lhermitte's syndrome (a transient demyelination syndrome of the spinal cord, which does not predict for subsequent radiation myelitis).

Late toxicity occurs 6 months or later after the completion of RT. It represents damage that is expressed at the end of the life cycle of parenchymal cells that have slow cell renewal and a relative inability to repopulate from stem cells. It occurs in organs that have less dependence on cell turnover and have both proliferative and functional cell populations, primarily connective and nervous tissue. Examples are the endothelium of blood vessels, and osteoblasts and chondroblasts of bone. These injuries are characterized by fibrosis, often over many years, and are not reversible, thus of serious consequence. It is essential to factor these risks into dose limitations. They are strongly correlated with fraction size, and the type of radiation used (Fig. 26.11).

A method of quantifying the risk of permanent tissue damage is the concept of TD5/5, which is the total dose, given in standard fraction sizes, that produces a 5% risk of damage to a specified organ at 5 years.⁷ These figures have been updated to reflect modern conformal treatments⁸ and provide a working model based on pooled data to constrain the dose to an organ at risk during the treatment-planning process, as well as for guiding informed consent.

Ionizing radiation kills cells by damaging DNA either directly or indirectly. Direct action disrupts DNA, and can

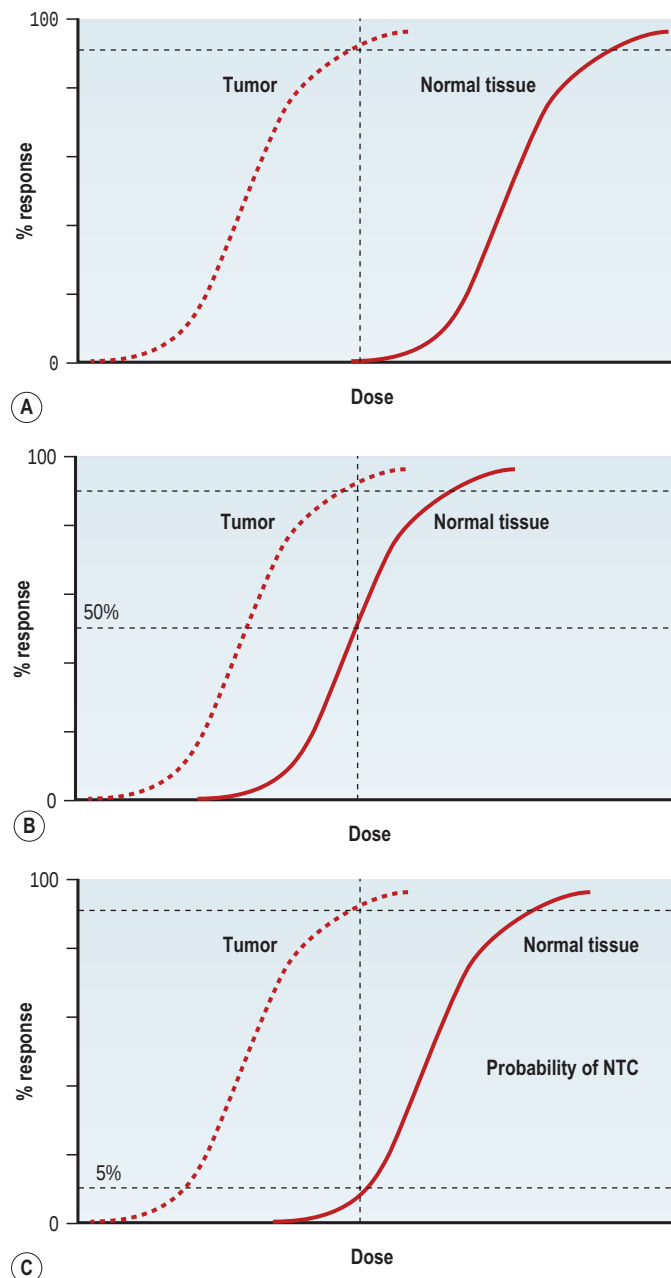


Fig. 26.8 Therapeutic ratio curves. (A) In an ideal situation, a tumor response would be almost complete before causing any tissue reaction. (B) More commonly, the dose required to achieve adequate tumor response also causes an unacceptably high risk of normal tissue reaction. (C) An acceptable trade-off is one that allows adequate tumor control and less than 5% probability of normal tissue complications (NTC).

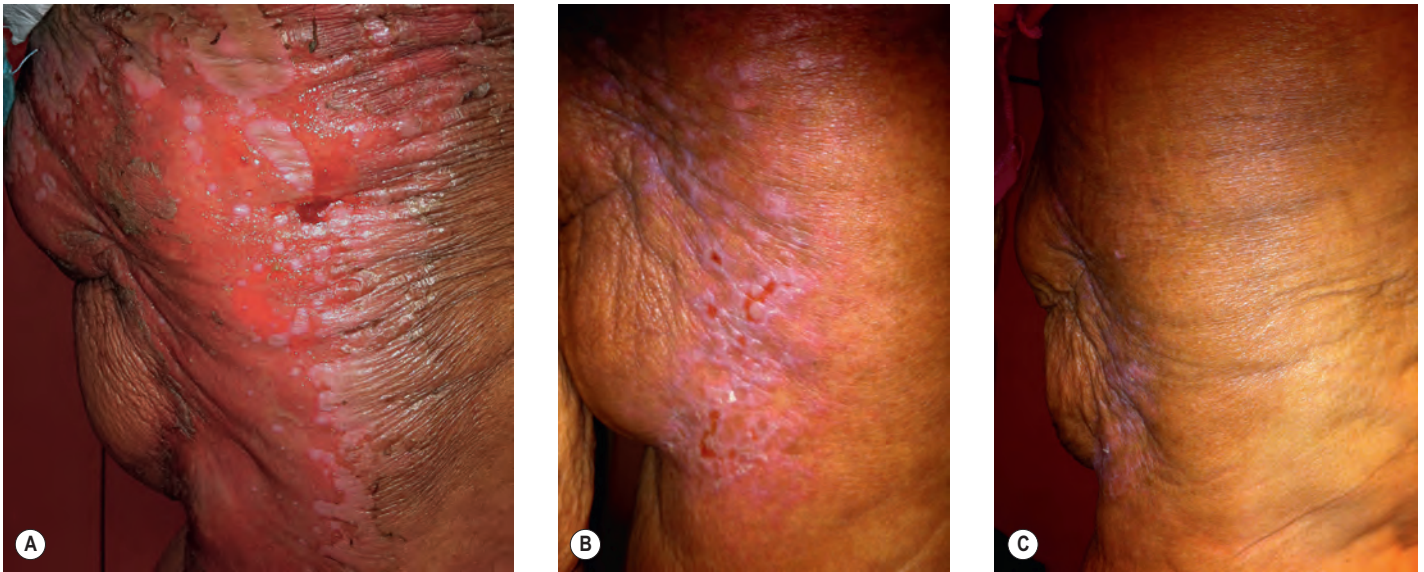


Fig. 26.9 Acute skin reactions can be severe, depending on multiple factors, including the volume and total dose. (A) Clinical photograph of the posterior thigh of a woman with a large (28 cm) sarcoma, treated with postoperative radiation to a total dose of 66 Gy. She had a history of over 240 lb (109 kg) intentional weight loss, and had marked skin redundancy, resulting in multiple folds, exacerbating her acute reaction. (B) Rapid improvement after just 7 days of conservative management with application of saline soaks. The white patches are healthy islands of new skin. (C) 14 days post completion of XRT.

cause lethal double-strand breaks. Indirectly ionizing radiation, which includes photons and neutrons, can cause damage by producing charged particles that then disrupt the DNA, but the damage is generally through indirect action, caused by the release of reactive oxygen species. Cell death can take several forms. Lethal chromosome damage can result in cellular death or loss of reproductive capacity. Apoptosis is a type of programmed cell death associated with activation of the tumor suppressor gene *p53* and is rapid, inducing no inflammatory response. Although it has been described in many different tissues, only certain tumors, such as

hematopoietic cells, primarily undergo apoptotic death. The commonest mechanism of cell death from radiation is through mitotic death when cells cannot divide because of damaged chromosomes. Another cellular response after radiation is senescence, in which cells survive and continue to function, but lose their capacity to reproduce and proliferate.

All organized tissues mount repair in response to injury. Radiation injury prompts the body to respond in a similar way as it does to other trauma, for example, surgery. However, there are three important differences. Firstly, radiation delivers a repetitive, daily injury during the course of fractionated

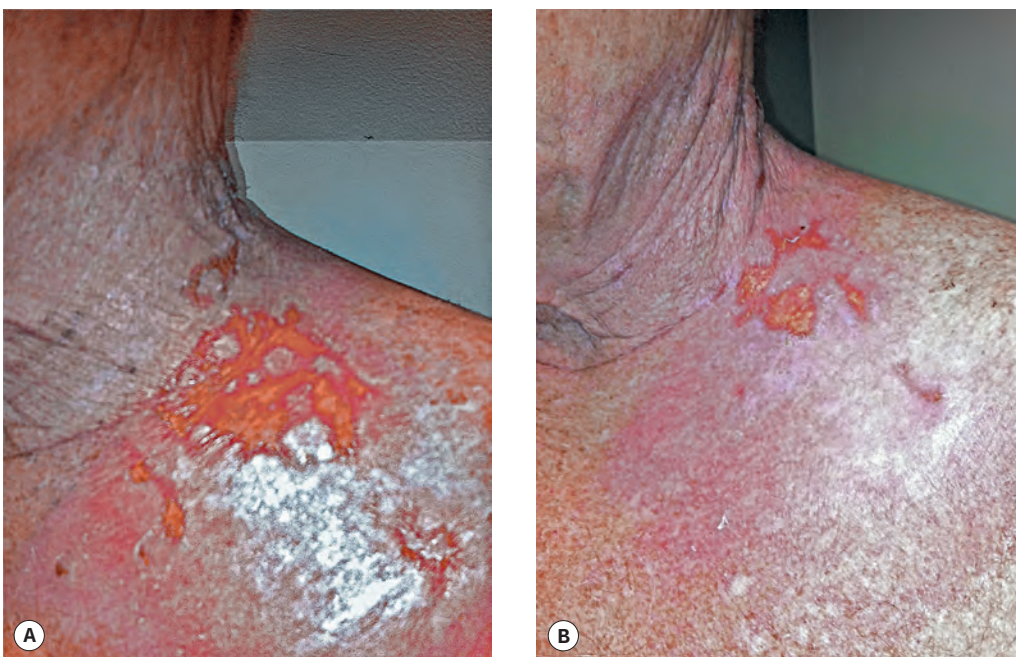


Fig. 26.10 Acute skin reaction in the neck. (A) An acute skin reaction at the base of the neck at a completion dose of 70 Gy. (B) 1 week later, again demonstrating rapid recovery and the skin islands. This reaction at the base of the neck is fairly typical, and is a result of the obliquity of the surface and narrowness of the shoulder.

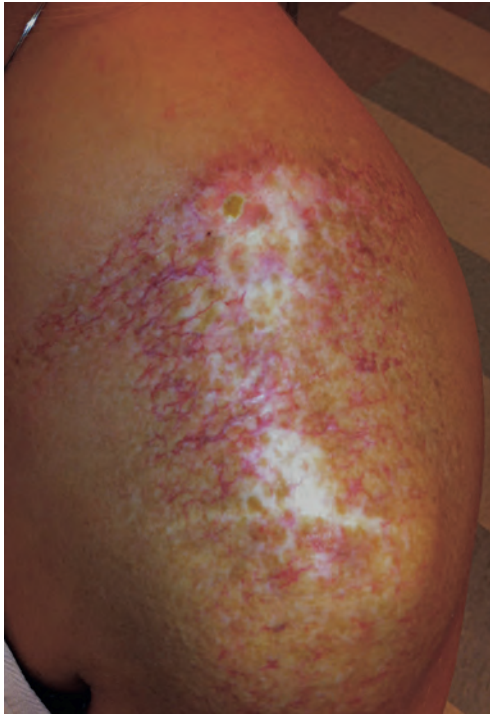


Fig. 26.11 A severe late skin reaction as a result of fast neutron therapy 22 years earlier following excision of a large dermatofibrosarcoma protuberans (DFSP) tumor from the shoulder. It demonstrates characteristic telangiectasia, hypopigmentation, subcutaneous fibrosis and, medially, delayed healing of a minor skin abrasion.

treatment. Secondly, the injury caused by the release in the tissue of free radicals affects all cellular and extracellular components within the volume of tissue irradiated. Thirdly, radiation causes damage to the DNA.

Response to radiation injury causes a signal transduction pathway that is mediated by the ataxia telangiectasia mutated (ATM) gene to instigate DNA repair and to regulate cell cycle checkpoints, giving the cells additional time to repair. A cascade of cytokines is an immediate response, and may lead to both radiosensitization and protection.⁹ Interleukin-1 and 6, and tumor necrosis factor- α cause an inflammatory response and coagulation effect. Transforming growth factor- β (TGF- β) is one of the most widely studied radiation-induced cytokines, and plays multiple roles.¹⁰ It causes fibroblast differentiation as well as stimulating the production of collagen. It is involved in the synthesis and regulation of extracellular matrix molecules. Following radiation, the extracellular matrix is both quantitatively and qualitatively modified – degrading processes are altered and production of collagen synthesis increases. TGF- β also down-regulates thrombomodulin activity in endothelium, leading to platelet aggregation, and, from the platelets, release of more TGF- β , thus setting up a self-perpetuation production of TGF- β that contributes to the chronicity of radiation injury. However, it is primarily the sustained activity of TGF- β -driven myofibroblasts that causes the fibrotic reactions to radiation. Fibrosis is not an endpoint, but a dynamic process of fibroblast activity. In traumatic wounds, remodeling happens over years, but this capacity to remodel is lost in irradiated tissue and instead there is self-perpetuating reactive fibrosis. As a result, irradiated skin and soft tissue are susceptible to minimal trauma, creating a problem for surgical intervention. Radiation causes delayed

wound healing, with decreased wound-breaking strength because of the damage to the microvasculature and the decreased cellular elements.¹¹ These problems are related to the total dose, the dose per fraction, the timing of the surgery, and the extent of the surgery. The optimal time to operate on irradiated skin is the window provided once the acute reaction has resolved and before the development of excessive fibrosis, generally 3–10 weeks after completion of X-ray therapy (XRT).

Applications

Radiation treatment-planning and process

The preparation for radiation treatment, or planning, starts with a decision on the treatment intention – curative, palliative, or optimization of local control (complex palliation) – and the probable dose prescription. Following informed consent, the patient is simulated for the treatment. Simulation is the radiation oncologist's equivalent to the operative day, allowing dedicated time to accurately map out the areas for treatment. Two-dimensional planning with fluoroscopy has now been mostly replaced by a three-dimensional approach, using diagnostic-quality CT scan with contrast (intravenous and oral as necessary). The scanners are equipped with a flat, as opposed to concave, couch, and the bore is often extra-wide, to accommodate the proposed treatment position, such as arms above the head, or legs separated in a frog-leg position. To achieve a reproducible position, immobilization devices are made. The type of device depends very much on the treatment site. To treat the head and neck region, a mesh acrylic mask, similar to the type of mask worn by burn patients requiring compression treatment, is formed exactly to the patient's face and head with eye, nares, and mouth openings (Fig. 26.12). This not only allows reproducible positioning but also obviates the need for tattoos or other skin markings in visible areas. Extremities are immobilized using casts of the

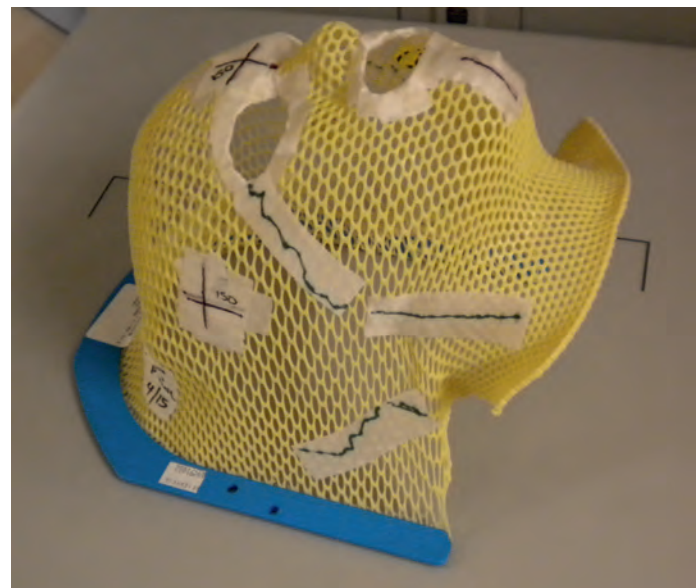


Fig. 26.12 A mask to immobilize the head and neck in a reproducible position.

same material and body immobilization is achieved with the use of vacuum splints and bags. All of these devices are referenced to the couch position. Once the position is confirmed, immobilized, and referenced, the patient then has a CT scan in this position and goes home. These images are imported into a radiation treatment-planning system.

Using the original diagnostic scans, and often fusing them with the planning CT, the radiation oncologist starts delineating all the structures of interest on every CT slice as it is displayed on the workstation. Any visible tumor is delineated as one or several gross tumor volumes (GTV). These are then encompassed by one or more clinical target volumes (CTV), which include normal-looking tissue considered by the radiation oncologist to be at high risk of containing tumor cells. Defining this volume, and deciding on its dose, require judgment of risks and benefits, and are central to the discipline of radiation oncology. It is possible to have several CTVs that require different doses, depending on the likelihood of tumor burden. The CTV is then expanded to form a planning target volume (PTV) that accounts for measured movement of the tumor or organs, for example, to account for a lung mass moving with respiration, as well as other calculated variations.

The next step is to identify and contour all organs at risk (OAR), that is, those normal tissues that are sensitive to radiation – examples include kidneys, spinal cord, and femoral head. Each of these sensitive structures is identified with a dose constraint. The result is a three-dimensional digital representation of the patient, tumor, and organs at risk. Working with dosimetrists, a treatment technique is decided by placing multiple beams through a series of protocols to determine the optimal beam arrangement to cover the target volumes homogeneously to the prescribed dose while sparing critical structures. Dose volume histograms calculate constraints for the OAR, for example, in the thorax, the V_{20} refers to the percentage of cancer-free lung (i.e., without the CTV) that receives >20 Gy; if this is above 35%, it is strongly predictive for radiation pneumonitis. This aspect of radiation treatment planning, rather than just positioning the patient on the CT bed, is the heart of the simulation process.

Once the radiation treatment plan has been designed, it is checked by a physicist for quality assurance to ensure that the plan is technically feasible on the treatment unit, and that no further beam modification is necessary. The patient returns for a dry run of the plan, and verification of set up. During this session the patient is repositioned in the immobilization device on the treatment machine, and, using light beams, the geometric parameters are checked. Verification includes comparison of the portal imaging to the digitally reconstructed radiographs (DRR) from simulation to ensure that the isocenter of the fields, the field shapes, and the shielding are consistent with the plan. If all parameters set up correctly, the patient is tattooed to facilitate accurate placement on the machine on subsequent visits. If there are any problems, adjustments are made before the patient returns the next day for the start of actual treatment. Further verification is done with cone beam CT, and adjustments, or shifts, are made as necessary, and usually repeated on a daily basis. Image-guided radiation therapy (IGRT) thus verifies that highly conformal plans are delivered not only accurately, but also with

Clinical applications

Units of radiation

The unit of absorbed radiation dose is the gray (Gy), corresponding to 1 joule of energy per kilogram of tissue. One gray equals 100 cGy. SI units that are named after people are, by SI convention, lower case when the whole name is used, but capitalized when the abbreviation is used. The gray replaced the older unit rad. One rad is equivalent to 1 cGy.

Treatment intention and dosing

The dose is determined by the intention of the treatment. Radiation can be used as the primary modality of therapy or combined with surgery and chemotherapy. When the treatment intent is curative, radical doses, such as 66 Gy for early (and 70 Gy for late) laryngeal cancer or 80 Gy for prostate cancer, are delivered in standard fractionation sizes of 1.8–2.0 Gy per daily fraction, 5 days a week, over periods of 7 weeks or more. Typically, the maximum dose is applied to known tumor, but lower doses (45–50 cGy) are used to treat tissues that have the potential for microscopic disease, for example, the peritumoral edema around a soft tissue sarcoma. However, when resection margins are histologically positive, a higher dose is needed, e.g., to 70 Gy, and the context is no longer adjuvant.

In noncurative situations, treatment may be used to palliate symptoms such as pain or bleeding, employing hypofractionated regimens that use smaller total doses but a larger dose per fraction. A common palliative course would be 20 Gy delivered in 5 fractions of 4 Gy. However, there are also noncurative situations when a patient has known metastatic disease, but bulky or aggressive tumor at the primary site that is, or will shortly become, very symptomatic and impair quality of life. Radical radiation approaches are used to optimize local control, for example, an unresectable fungating breast cancer even in the presence of bone metastases.

Dose can also be hyperfractionated, when smaller fractions are given twice a day, so that treatment can be accelerated, potentially improving tumor cell kill and causing less repopulation of very fast-growing tumors. This can also be a way to protect normal structures from late irreversible toxicity, especially in high-risk situations like retreatment. Hypofractionated RT with a large dose per fraction, but fewer fractions, has traditionally been reserved for palliative RT, as described above. However, when the volume is small, the risk of late toxicity is low, and the high dose is ablative, treatment can be curative, as in SBRT, described earlier. It is also increasingly used in oligometastatic situations for patients with good performance status and a small burden of metastatic disease that is chemosensitive, as this approach can improve survival, and may have an abscopal effect.^{12,13}

Patient selection

As in any branch of medicine, careful patient selection and informed consent are essential. Patients are often referred to radiation oncology when surgery or chemotherapy options are not feasible because of comorbidities or poor performance status. There are some basic principles to follow. For all patients, but particularly for young people, potential benefit of radiation must be weighed against the late sequelae of

radiation, including the risk of second malignancy. Poor performance status and patient preferences can shift a potentially curative scenario into one of observation, or nonradical radiotherapy. However, chromosomal fragility syndromes such as Li–Fraumeni syndrome and Rb or ATM gene carriers are contraindications to radical or curative RT. Previous RT is only a relative contraindication, in that it may be possible to give a palliative dose, or even to treat to radical doses using stereotactic techniques to treat small volumes.

Hints and tips

- For all patients, but particularly for young people, potential benefit of radiation must be weighed against the late sequelae of radiation, including the risk of second malignancy.
- Chromosomal fragility syndromes such as Li–Fraumeni syndrome, and Rb or ATM gene carriers, are contraindications to radical or curative radiation therapy.
- Previous radiation therapy is a relative contraindication.

Breast cancer

Until 1997, it was widely believed that XRT for breast cancer only offered local control, and that any improvement in survival was related to the effect of adjuvant systemic therapy. Any survival advantage of radiation was negated by deaths that may have been caused by cardiotoxicity from large fractions and older, less precise techniques. Two landmark studies examining the role of RT in node-positive breast cancer demonstrated significantly improved survival with RT and changed breast cancer practice dramatically.^{14–16} The impact on overall survival has been confirmed in subsequent meta-analyses.^{17,18} Although not as dramatic a finding as for nodal XRT, radiation to the intact breast alone also confers a small survival advantage.¹⁹

Breast conservation

Adjuvant breast irradiation allows breast conservation by reducing the risk of breast cancer recurrence. The evidence for the effectiveness of postlumpectomy radiation is strong, and derived from many randomized clinical trials,²⁰ and provides equivalent²¹ or even improved²² survival for younger women in modern series. It is one of the commonest radiotherapy treatments in RT practice. Cosmesis was also found to be satisfactory in a large European study that used rigorous assessment methods.²³ It is contraindicated when there has been previous radiation treatment to the breast or chest wall (e.g., in the treatment of Hodgkin's lymphoma), during pregnancy, or when the margins are positive. Women with active connective tissue disease, especially scleroderma,²⁴ may have an increased risk of acute and late toxicities, and woman with large tumors may have poorer cosmesis as a result of a larger defect. These, however, are only relative contraindications.

Indications for postmastectomy radiation (PMRT)

PMRT is indicated for circumstances where the tumor is 5 cm or larger; when the margins are positive, or closer than 1 mm; or where there are regional lymph node metastases, since these

are all strong predictors of chest wall recurrence. Radiation should also be considered when the lymph node status is uncertain, and the histology shows that the tumor has evidence of lymphovascular involvement, which predicts for local recurrence.^{25,26} Conversely, it is not indicated when the tumor size is less than 5 cm with negative margins and without spread to the lymph nodes. There is even evidence to suggest that tumors of 5 cm that are N0 do not benefit from PMRT.²⁷

Radiation of the nodal draining areas

Nodal irradiation is indicated when four or more lymph nodes are positive; RT for 1–3 nodes is still a gray area, even though it has become fairly routine practice. When there has been an adequate sampling, the upper axilla is usually not included in the volume, although the supraclavicular area, i.e., the next echelon of nodes, is included. Internal mammary (IM) nodal RT is controversial, and subject to institutional bias.²⁸ IM nodal involvement is known to be more common in medial and central breast cancers, and to be present when axillary lymph nodes are positive,²⁹ although IM clinical failure is rare. Positive IM nodes detected on imaging such as positron emission tomography (PET) fludeoxyglucose scan are rarely resectable, unlike axillary nodes, and thus need a higher dose of RT,³⁰ as this situation is no longer one of adjuvant therapy.

RT techniques

The target volume includes the breast, subcutaneous tissues, and chest wall. In any technique used to cover these tissues, the lower axilla is usually within the high dose volume. The classic technique is breast “tangents”, using medial and lateral beams (Fig. 26.13) that are either angled or blocked to reduce the dose to the heart and lungs. The beam can be modified



Fig. 26.13 Conserved breast treated with classic breast tangents, internal mammary chain (IMC) not covered.

with a wedge-shaped device to reduce the “hot spot” of radiation dose that can result from this technique. IMRT and other conformal approaches are frequently used now, obviating the need for wedges, providing homogeneous dose distribution and reducing treatment time.

The same techniques are used to treat the chest wall, although the scar and drains have traditionally been in the high-dose volume, necessitating bolus to ensure that the scar receives an adequate dose (Fig. 26.14). The use of bolus on the entire chest wall is debatable, except in the case of inflammatory breast cancer, where tumor cells, by definition, invade the dermis, and so it is essential to achieve full dose on the chest wall skin.

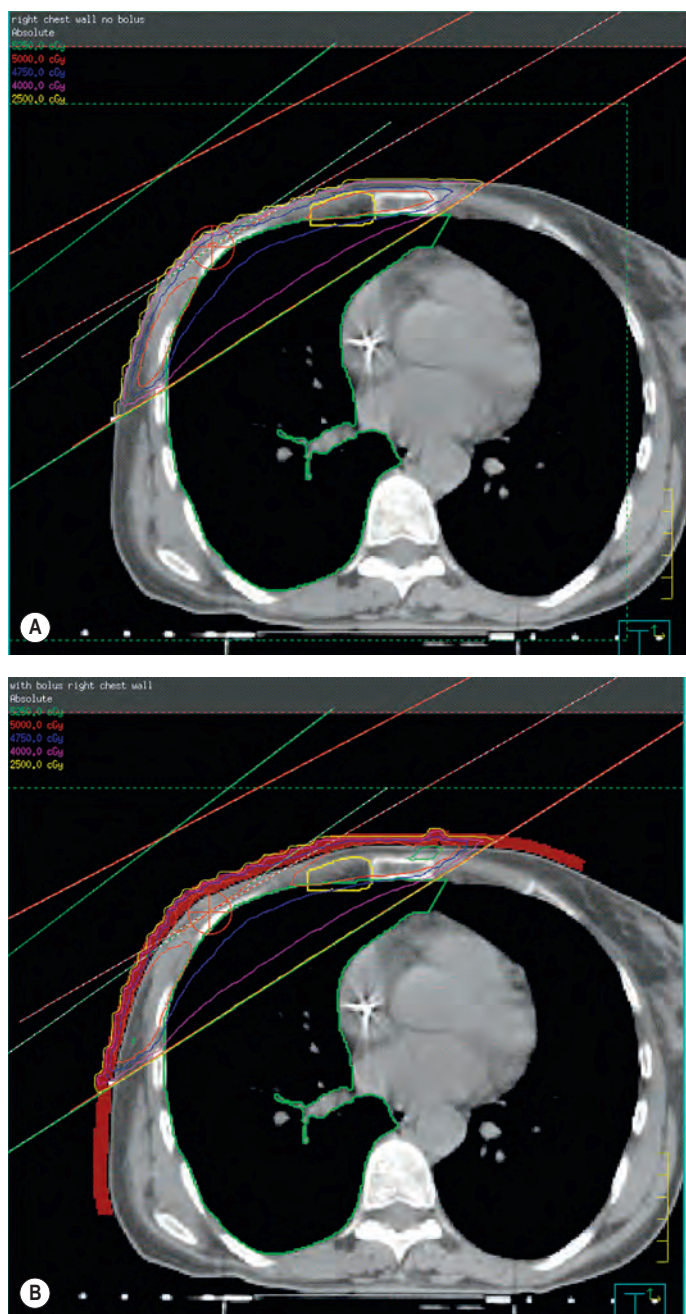


Fig. 26.14 Post mastectomy XRT plan. (A) Including the IMC nodal area using a wide tangent technique, resulting in a larger volume of irradiated lung. (B) The use of bolus to bring the surface dose to 100%, and losing the skin sparing effect.

Apart from the lower axilla, which is incidentally covered in breast or chest wall techniques, additional planning is required to ensure that the targeted lymph node areas match carefully to the breast/chest wall volumes to avoid overlap and increased toxicity to the normal tissues, including the brachial plexus. The small apex of the ipsilateral lung receives a full dose when treating the supraclavicular lymph node. If overlap of fields happens, a portion of the brachial plexus may receive almost a double dose of radiation, and thus be at very high risk of brachial plexopathy. If treating the IM nodal chains, there are two main techniques: the first uses an extra-wide tangent arrangement, which can result in a significantly larger volume of lung tissue being damaged. The addition of an electron field patched on to the medial aspect of the tangent fields delivers a fairly homogeneous dose over the IM nodes, despite increasing lung and also cardiac dose, if the tumor is located on the left side. Getting adequate dosing into the IM nodes, and avoiding critical structures, can be especially challenging when an expander has already been placed in the chest wall prior to using this technique (Fig. 26.15), sometimes causing the electron dose to “splash” on to the contralateral breast. This does not happen often on the flat chest wall of PMRT, or when the breasts are natural and fall to the side, leaving the ipsilateral parasternal area flat.

The standard adjuvant dose to the chest wall or breast ranges from 45 to 60 Gy, given in 1.8–2 Gy/fraction, depending on practice, with the same dose used for the nodal areas. As a result of a Canadian study in early-stage breast cancer, hypofractionated RT prescribing 42.5 Gy at 2.66 Gy/fraction provides the same local control as more prolonged treatment schedules. Despite the larger dose per fraction, cosmesis remains acceptable on long-term follow-up.^{31,32}

Even in the absence of positive margins, local recurrence is most likely to occur in the operative bed, or tumor cavity. The use of a boost to this volume can reduce this risk, and is recommended in patients at higher risk for local failure (age <50 years, positive axillary nodes, lymphovascular invasion, or close margins). A European study³³ showed that women aged 40 or younger benefited significantly from extra treatment to the tumor cavity, halving their risk of local recurrence from 19.5% to 10.2%. The benefit was less striking in women aged over 40. Boost doses of 2 Gy/fraction usually bring the total dose to the tumor cavity to a minimum of 60 Gy, and can be delivered with photons, including using conformal or IMRT techniques, electrons, a combination of photons and electrons, brachytherapy, or, more recently, with protons. The technique again depends on institutional experience and operator skill. Addition of a boost can result in fibrosis and compromise cosmesis.³³

Another approach has been to treat only the area most at risk, i.e., the cavity plus a margin, and not treat the whole breast. Accelerated partial breast irradiation seems to provide equivalent local control in patients over age 60 years, with low risk features, in a very convenient fashion with 10 b.i.d. treatments of either brachytherapy (total 34 Gy) or external-beam photon therapy (total 38.5 Gy) to the tumor bed.

Head and neck cancer

Head and neck cancers are mostly squamous cell carcinomas (HNSCCs). Radiation has an important role in the primary, postoperative, and palliative aspect of their management.

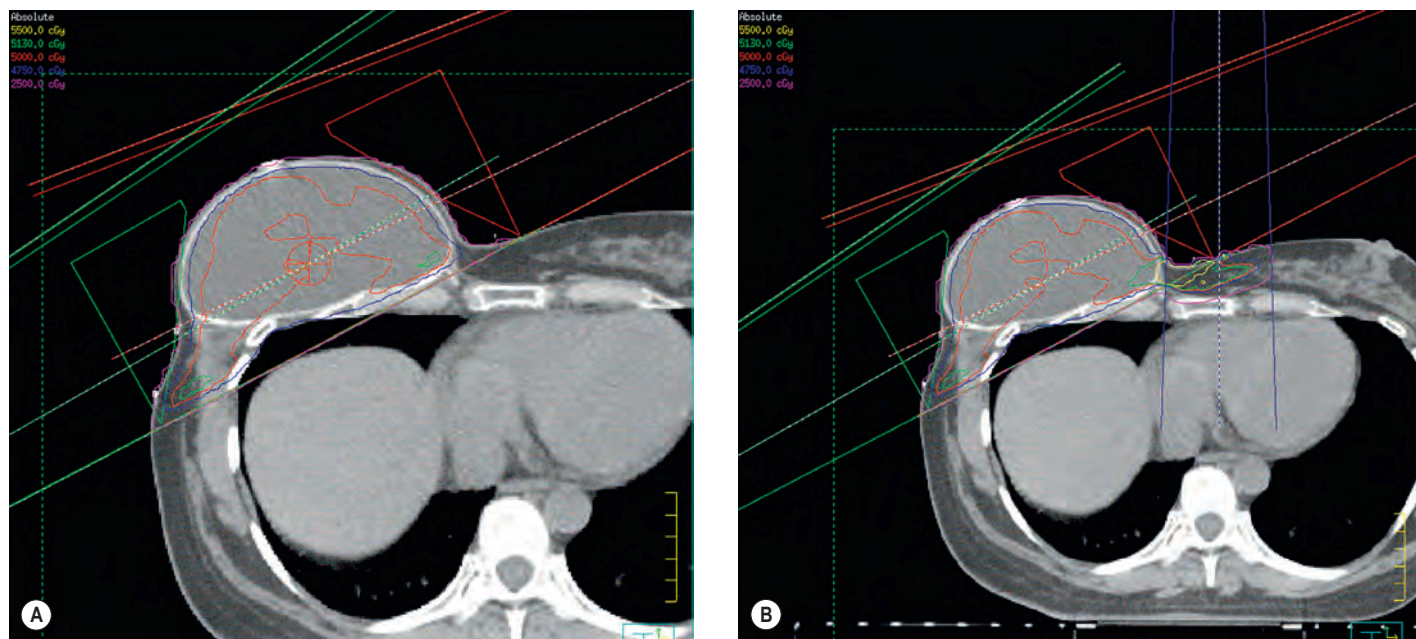


Fig. 26.15 (A) Treating a right breast mound with inflated expander in place can mean that the medial aspect of the contralateral breast may be “splashed”. (B) The expander *in situ* is more problematic for the contralateral breast when the IMC lymph nodes are treated.

Previously, a general principle of minimizing toxicity by using either surgery or radiation, and keeping the other modality for salvage, was preferred. However, increasingly, especially in locally advanced disease, combined modality, particularly postoperative radiation treatment, is used because it has been shown to reduce the incidence of recurrence, especially in the cervical lymph nodes. The use of concurrent chemotherapy has also changed the practice over the last 10–15 years. Several studies have shown a benefit in both survival and local control,³⁴ as a result, platinum-based therapy has become the standard of care in the management of all but the most favorable – early disease that has a high cure rate with RT alone. However acute toxicity is considerably worsened by concurrent chemotherapy, and some patients are not optimal candidates for cisplatin due to competing comorbidities or poor performance status. In RTOG 9501,³⁵ cetuximab concurrently with radiotherapy for locally advanced head and neck squamous cell carcinomas showed an improvement in survival and local control compared to radiation alone and appeared to have less toxicity compared to cisplatin based on historical trials.

The incidence of HPV-associated oropharyngeal cancers has been increasing, with a decrease in rates in smokers. HPV-associated oropharyngeal SCC clinically behaves differently with a better prognosis. De-intensification of therapy for HPV-positive tumors is being investigated in multiple ongoing trials with the overall goal to reduce morbidity in HPV-related HNSCC without a detriment in survival and local control. Data from these studies will help guide optimal treatment in this patient population.

SCC head and neck cancers have lower local control rates if treatment time is extended, due to repopulation of tumor cells.³⁶ In order to overcome this effect, efforts have to be made to deliver five fractions per week even if it requires treating twice a day to do so. Approaches that intensify the course of treatment by giving it over a shorter period of time (accelerated fractionation) or giving treatment more than once a day using

a smaller dose per fraction over the same time period (hyperfractionation) can improve outcome but result in severe acute toxicity so that breaks in treatment may be necessary, thus negating the benefit of altering the fractionation schedule.

Doses used for gross tumor are in the 66–72 Gy range. Subclinical disease is treated to 50–60 Gy. Before the introduction of IMRT, these areas were usually treated sequentially, covering the larger volume to a “microscopic” dose, before boosting the smaller volume or volumes containing gross disease, although a concomitant boost was sometimes used. However, IMRT allows a technique of “dose painting” or differential dosing so that the areas at higher risk are programmed to receive a slightly higher dose per day than the areas of low risk. It can also reduce the dose to the parotid, reducing the risk of permanent xerostomia.³⁷ Submandibular gland-sparing IMRT has also been utilized in select patients to reduce xerostomia with excellent locoregional control.³⁸

Acute toxicities occur during the course of treatment and resolve 2–3 months following completion of treatment. They are reversible unless the acute damage is confluent, causing damage to the basal membrane and depleting the supply of stem cells. Mucositis, which is exacerbated by smoking and alcohol, starts during weeks 2–3, becoming confluent by the end. It affects the mucous membranes within the high-dose volume and results in difficulty in swallowing. Because of concerns about nutritional status, percutaneous endoscopic gastrostomy tubes are inserted before the start of treatment. Mucositis is painful and mouthwashes containing local anesthetic help this, but usually narcotics are also required. The skin develops erythema by weeks 3–4, even with the aggressive use of topical aloe vera gels, other unguents, and steroids. Reaction is inevitably brisk with moist desquamation by completion of treatment. Because of dose to the parotid, patients will also experience change in taste; radiation causes xerostomia, changing the consistency of saliva by drying the water component, which results in thick mucoid secretions

that are difficult to clear. During treatment patients often lose weight and experience fatigue.

Late toxicities depend on the size of dose per fraction given. They occur 6 months to 3 years following the completion of treatment and unfortunately are permanent and progressive. The primary problem is fibrosis that can affect the subcutaneous tissues, musculature, and joints. The patient can experience trismus, neck stiffness, aching, and swallowing difficulties as a result. If the parotid has been treated to more than 26 Gy the patient may be left with permanent xerostomia, which can exacerbate dental problems. The patient may also experience voice changes due to chronic laryngeal edema and/or cartilage damage. Patients are also at risk of osteoradionecrosis (ORN), as described later.

Soft-tissue sarcoma

Sarcomas comprise a heterogeneous group of more than 100 bone and soft-tissue mesenchymal subtypes. Soft-tissue sarcomas (STS) are rare mesenchymal malignancies arising from connective tissue. They can arise anywhere in the body but most commonly affect the extremities and trunk. In the pediatric population, 7% of tumors are STS,³⁹ with half of these being rhabdomyosarcoma, and, especially in younger children, these tumors are more responsive to chemotherapy, so radiation is either spared or used at lower doses to avoid arresting growth or increasing the risk of a second malignancy.

Because of the rarity of STS (only about 10 000 are diagnosed per year in the US) and the numerous locations and subtypes, they are best managed in specialized multidisciplinary groups that include dedicated sarcoma radiation oncologists. Prognosis depends on size, grade, histological subtype, and superficiality of the tumor. Location is also important; retroperitoneal sarcomas have an independently worse outcome, but usually do not present until tumors are very large.

Although the primary treatment of STS is surgery, adjuvant radiation is important for limb and function conservation in extremity sarcoma and reducing the risk of local recurrence. Overall, local control rates are approximately 80% at 5 years.⁴⁰ If the patient is unfit for surgery, primary RT can provide useful local control. The role of XRT in adjuvant treatment of osteosarcoma, chondrosarcoma, and chordoma is minimal, although it can be a useful modality for palliation.

Doses and techniques in adults

Postoperative adjuvant XRT is indicated after resection of high-grade or large tumors with negative margins, or any tumor with positive margins.

Standard adjuvant postoperative radiation doses for STS are 60–66 Gy in 30–33 fractions, or higher if any gross disease remains, with reduction in the size of the volume after 50 Gy. The CTV is often large, encompassing the entire operative bed, which is determined with postoperative magnetic resonance imaging (MRI) to visualize the operative “footprint”, or by reconstructing preoperative imaging (e.g., fusing with diagnostic MR scan) and using surgical clips, operating room report, and guidance from the surgeon to determine the extent of the target volume. Generous margins are used to cover any uncertainty.

The standard preoperative neoadjuvant XRT dose is 50 Gy given in 25 fractions of 2 Gy over 5 weeks. The GTV covers

the radiologically visible tumor and the CTV covers peritumoral edema as seen on MRI T2 imaging, or CT or PET CT volume plus 2–3 cm. If the margins are positive after resection, a further 16 Gy is usually given, although this practice may not be necessary.⁴¹

Optimal immobilization is important in the RT planning process. It is also necessary to delineate bones, joints, and perineum so that dose to these sites can be minimized. It is also necessary to spare a longitudinal strip of skin and subcutaneous tissue so that lymphatic drainage remains intact to reduce the risk of chronic lymphedema. Conformal techniques, including IMRT, are often needed to meet these constraints.

The issue of whether pre- or postoperative XRT is used remains controversial. Certainly the preoperative advantages of an early start of XRT, a smaller irradiated volume and likely lower dose, and, as a result of these features, less fibrosis and better functional outcome⁴² are compelling. However, the delay to definitive surgical treatment and the doubling of risk of wound complications (17–35% in the Canadian randomized trial) are also serious issues to consider.⁴²

Skin cancers

Nonmelanoma skin cancers

This group encompasses basal cell carcinoma (BCC), SCC, Merkel cell carcinoma, and cutaneous angiosarcoma. Of these, the commonest are BCC and SCC. The majority are radiation-related, albeit mostly solar radiation! Due to their chronic immunosuppression, patients who have undergone transplantation are more likely to develop SCC, which tends to behave more aggressively. Primary radiation is indicated when the patient is not a surgical candidate (due to comorbidities, anticoagulation, or patient preference) or when surgery may risk function or cosmesis, and in the adjuvant setting to reduce the risk of local recurrence. It can provide good palliation for locally advanced unresectable disease, often with high doses to optimize local control. Decisions about the extent of the RT target volume are based on the risk of lymph node metastases, and inclusion of the regional nodes in high-risk disease. An important consideration is the presence of perineural invasion, which may involve treating extended volumes along neural pathways. In all, 30–40% of incompletely incised BCCs recur but they can be salvaged equally with surgery or radiation.⁴³ Doses for the primary treatment of BCC are in the range of 40–50 Gy delivered in 10–20 fractions, but higher doses are needed for SCC, similar to those for head and neck squamous cell cancers. Small lesions without risk for nodal or perineural involvement can be treated with hypofractionation.

When delivering radiotherapy for skin cancers one has to be able to achieve a high dose superficially. One of the best ways to do this is to use superficial kV equipment that provides 100% of the dose at the surface and a very tight penumbra resulting in smaller fields. However, this equipment has now been largely supplanted by electrons, which have a larger penumbra due to their propensity to scatter. Furthermore, low-energy electrons do not provide 100% of the dose at the surface, which is corrected with the use of bolus.

Although treatment with XRT is highly curative, late toxicities of treatment result in cosmetic changes related to change

in pigmentation, fatty necrosis, subcutaneous fibrosis, and dermal telangiectasia. These tend not to arise for 2 years or more after treatment and not all patients suffer these effects. These risks are increased with larger volumes and larger fraction size. Fortunately, since many of these cancers are small, and the patient population is, by and large, elderly and frail, one can still get away with using hypofractionated treatment over a shorter period of time.

Merkel cell carcinoma is a rare neuroendocrine skin tumor that has a lethal potential for spread. Both the local disease and the regional lymph nodes need to be treated. Inclusion of nodal areas means that radiotherapy volumes become larger and smaller fraction sizes are necessary. However, hypofractionation with single fraction has been shown to provide excellent control with possible abscopal effects.⁴⁴

Angiosarcoma is primarily treated with surgery. When this is not possible or when there is recurrence or presence of positive margins, radiation is necessary with higher doses between 66 and 70 Gy. Tumor location can be an important issue in planning treatment. Treating the entire scalp but avoiding the brain requires sophisticated treatment planning. One technique is called the "German helmet", in which a combination of photons and electrons is used to minimize penetration to the brain and subsequent cognitive dysfunction.

Malignant melanoma is generally thought to be relatively radioresistant. *In vivo* studies show that the cell survival curve has a very broad shoulder, indicating that these cells have a large capacity to repair sublethal damage. The way to overcome this is to hypofractionate with large doses per fraction. Adjuvant radiation can reduce the risk of local recurrence in high-risk adjuvant situations. At the MD Anderson Cancer Center, criteria for this include desmoplastic histology, depth >4 mm with ulceration or satellite lesions, positive margins, or recurrent disease.⁴⁵ Radiation to involved or high-risk but clinically negative lymph nodes can improve control. Hypofractionated radiotherapy is effective, 6 Gy twice a week for a total of 30–36 Gy regimens such as are commonly used,⁴⁶ albeit with a higher risk of lymphedema, improving local control from 50% to 87%⁴⁷ without affecting survival. Radiation also plays a major role in palliation of brain and bone metastases, and uncontrolled tumor.

Benign disorders

RT was historically used to treat many benign conditions, such as ankylosing spondylitis, tinea capita, and eczema, that fortunately now are treated with other therapies. However, it is still used in the treatment of noncancerous conditions such as prevention of heterotopic ossification after hip replacement surgery and keloid scars.⁴⁸ Doses used are low, so unlikely to cause significant problems with fibrosis. However, especially in a younger person, the concerns about development of a radiation-induced malignancy must be weighed against the potential gain of using radiation for benign disease.

Specific toxicities and complications

Bony injury

ORN is a necrotic wound manifested in irradiated bone that persists without healing for 3–6 months, in the absence of

tumor recurrence.⁴⁹ It presents as clinically exposed bone, sometimes without any pain, and radiologic evidence of necrosis on both CT and MRI between 1 and 3 years following radiation. Radiologic findings may mimic disease recurrence. ORN is mostly seen as a result of treating head and neck cancer and most frequently affects the mandible. Radiation-related risk factors include fraction size (>200 cGy), the volume of bone irradiated, a total dose to the bone of >6000 cGy, and re-irradiation. The modality of radiation used is also important, because particle therapy (electrons, neutrons, and protons), brachytherapy, and kilovoltage energy can result in higher absorbed doses within bone than from megavoltage XRT, e.g., photons. The use of three-dimensional treatment-planning systems, improvements in immobilization, as well as conformal techniques such as IMRT and higher precision with IGRT for localization, help to minimize the volume of bone in the target, as well as the dose. Other risk factors in the head and neck region include poor oral hygiene and dental extraction, making careful dental preparation an integral part of treatment planning. Prior to initiation of radiation therapy, patients undergo dental clearance. Dental extractions, if indicated, are done prior to the start of RT. During RT planning, the radiation oncologist delineates the mandible, maxilla, and salivary glands and identifies dose constraints. After completion of radiotherapy, patients proceed with life-long daily fluoride treatments and maintain a pristine dental hygiene regimen. Concurrent chemotherapy causes mucositis and xerostomia, further increasing the risk, as does the xerostomia resulting from relatively low doses to the parotid. ORN arising in other sites can also be associated with trauma and surgery.

Although ORN in the head and neck region had an incidence of 6.8% in 1968,⁵⁰ it is fortunately now quite rare, with recent series reporting incidences of 0–2%.^{51,52} Bisphosphonates can cause osteonecrosis without radiation,⁵³ but it is still unclear what increased risks are incurred with concurrent radiation and bisphosphonate therapies.

Bone fractures occurring within the irradiated volume are more common. Rib fractures tend to be the result of coughing. Limb fractures can happen with minimal trauma. No intervention is necessary for clavicles or ribs, but long bones usually require an intramedullary nail and there can be long delays in union. An analysis of fractures associated with soft-tissue sarcoma identified that the total dose to the bone and the volume irradiated were critical factors, leading to recommendations that the maximum dose to the bone should be 5900 cGy, and that the volume of bone receiving >4000 cGy be limited to 64%.⁵⁴

Bone growth in children

Prior to the development of effective chemotherapies, radiotherapy was the main modality in the treatment of pediatric tumors, so it was widely recognized early on that radiation impedes bone development in children, leading to limb shortening, asymmetry (including scoliosis), deformity and functional impairment. It was difficult initially to quantify dose constraints as treatments and dosimetry were very heterogeneous. Radiologically, there are changes on the growth plate that resemble rickets, with metaphyseal sclerosis, metaphyseal fraying, and epiphyseal plate widening, reflecting the radiosensitivity of rapidly proliferating cells in this region.

The child's age at the time of radiation is important, since most bone growth occurs in the first 5 years. The most important radiotherapy factors are the total dose and volume of bone irradiated. Although 30 Gy is considered the tolerance threshold dose, growth effects are seen with as low a dose as 15 Gy, suggesting a very steep dose–response curve in this range.⁵⁵ If the spine is within the high-dose volume, uniform dose across the whole vertebral body is recommended to reduce the risk of scoliosis.³⁹

Craniofacial growth is different to long bones, since these bones develop through intramembranous ossification, resulting in a complex three-dimensional pattern of growth.⁵⁶ Disruption of this growth by radiation in all or any part of the head and face can cause significant clinical problems, including distorted appearance and functional problems related to eating. Dentition is also affected.

Cranial irradiation is used for prophylaxis against central nervous system relapse in leukemia. Not only can this affect cognition and bone growth, it can also impair the production of growth hormone, which results in decreased bone mineralization.⁵⁷ Genetic factors are important, for example, in the treatment of retinoblastoma, where there may be much greater sensitivity to XRT. Biological factors that are disrupted by XRT include remodeling of the extracellular matrix in response to paracrine and endocrine signaling that affects chondrocyte production. Radioprotective agents, such as amifostine, have been studied *in vivo* and found to protect a number of cell lines, such as osteoblast-like, endothelial, and fibroblastic, from harmful effects of radiation.⁵⁸

Cardiovascular disease

There has been a well-established correlation between radiation and risk of cardiac morbidity and mortality, particularly associated with treatment of breast cancer and Hodgkin's lymphoma. Radiation therapy for left-sided breast tumors increases risk of subsequent ischemic cardiac disease by 7.4% per Gy mean heart dose that follows a linear, no-threshold relationship.⁵⁹ Several techniques have been developed to reduce heart and coronary vessel dose. Deep inspiratory breath hold (DIBH) is a technique to reduce the heart dose for left-sided breast cancer irradiation, with current data showing clinical benefit based on modeled risk estimates, most notably in patients with high baseline cardiac risk.⁶⁰ This technique displaces the heart away from the chest wall (Fig. 26.16). CT simulation involves both DIBH and free breathing scans for dosimetric comparisons of the heart and chest wall separation with breath hold technique.

Lymphedema

The mechanics of RT-related lymphedema are due to the radiation-induced fibrosis causing compression of the lymph vessels. When assessing lymphedema in someone who has had a previous cancer diagnosis, it is important to exclude recurrent disease before assuming that the edema is related to treatment. However, lymphedema after breast cancer is common. Norman *et al.* identified 42% 5-year accumulative incidence in a 5-year prospective, population-based study of breast cancer survivors. However, the majority (23%) described only mild lymphedema, and only 2% had developed chronic, severe edema.⁶¹

Independent risk factors for breast cancer-associated lymphedema include radiation treatment of the axilla, the extent of axillary lymph node dissection, the type of breast surgery, and the presence of regional lymph node metastases.⁶² A history of infection and injuries, and the patient's body mass index are also associated factors. The combination of XRT and axillary lymph node dissection confers the greatest risk.⁶¹ A large series from Massachusetts General Hospital reported lymphedema rates of 10% in women who had breast-conserving surgery and XRT to the axilla,⁶² although historically, higher rates have been reported. It has also been suggested⁵⁸ that, with survival and longevity, this late toxicity becomes more prevalent. However, as sentinel lymph node dissection has become the standard of care in early breast cancer, this will result in a lower risk of lymphedema than conventional axillary lymph node dissection risks.⁶³ ACOSOG Z0011 demonstrated that complete axillary lymph node dissection could be omitted in select patients with limited sentinel node-positive disease. This trial compared sentinel lymph node resection with versus without axillary lymph node dissection in patients with T1–2 tumors with up to 3 positive sentinel lymph nodes. All of the patients underwent

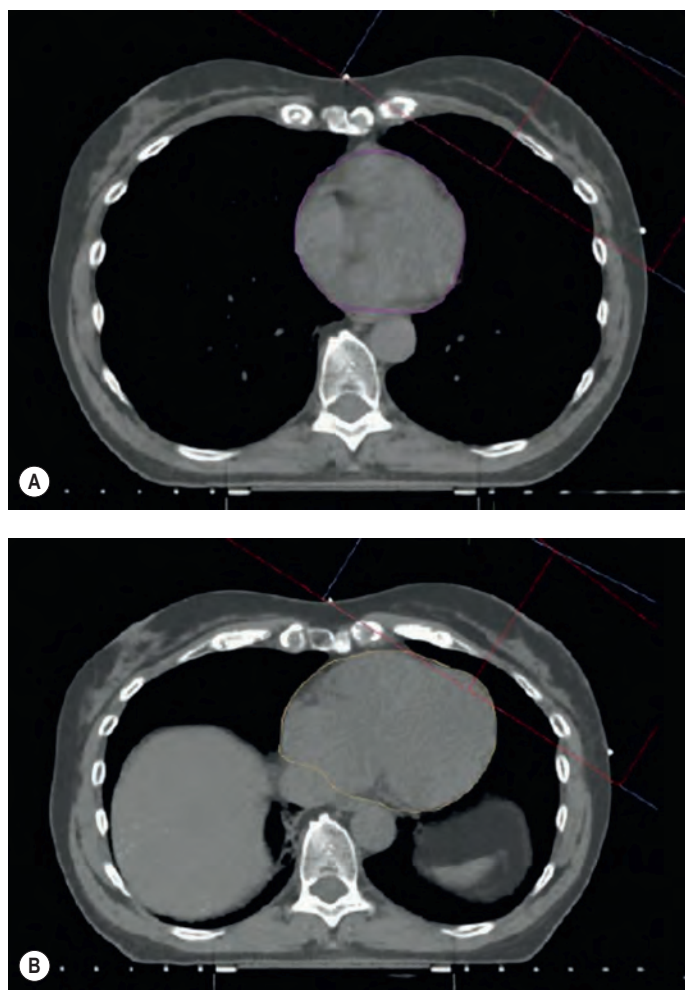


Fig. 26.16 Reducing dose to the heart in left-sided breast tumors. (A) Radiation treatment CT simulation for whole-breast irradiation with deep inspiratory breath-hold technique avoids the heart and coronary arteries in comparison to using standard free breathing (B). (Courtesy, L. Christine Fang MD.)

breast-conserving surgery with whole breast irradiation. The study required no dedicated axillary lymph node irradiation. There was no difference in local or regional recurrence, supporting omission of axillary lymph node dissection in this population.⁶⁴ Initial results of the AMAROS trial (which randomized patients with a positive sentinel lymph node to ALND or axillary RT) show excellent 5-year local control and survival with less lymphedema in the radiotherapy arm.⁶⁵

Brachial plexopathy

Brachial plexopathy is most commonly due to metastatic disease involving the brachial plexus, and it can be very difficult to distinguish between the late side effect of XRT versus recurrence. PET has been reported to be helpful.⁶⁶ However, it is also a rare (1%) complication of radiation treatment.⁶⁷ Its development is dependent not just on total dose, with a marked increase above 6000 cGy, but also on the dose per fraction. RT technique is also a very important factor, as older breast RT techniques that extended to the lymph nodes could result in overlapping fields just above the clavicle immediately above the brachial plexus, meaning that the plexus received up to twice the prescribed dose. Concurrent chemotherapy also increased the risk.

Radiation-induced malignancies

Radiation has been shown to induce malignant transformation *in vitro*, for example, in laboratory mice, and *in vivo*, for example, from atom bomb survivors, as well as long-term follow-up studies. Three mechanisms for radiation-induced malignancy have been suggested: (1) DNA damage and subsequent mutation; (2) disturbances of multiple defense or control mechanisms within the cell at the molecular level; and (3) the chronic ongoing damage of irradiated tissue.⁶⁸

Radiation-induced malignancies are rare within the first 5 years after treatment, and usually present many years after treatment. As more cancers are cured, and the number of long-term survivors increases, so does the risk of radiation-induced malignancies.⁶⁹ Although a second malignancy rate of 1 per 100 000 patients treated is often cited, this figure is only an estimate, and may be misleading. Many different mathematical models are used to standardize the doses, dose per fraction and quality of radiation, as well as the volume of the target, the organs treated, and the age of the patient. Second primary tumors are more common in those who have already had a malignancy, with a RR of 1.12, regardless of treatment. Chemotherapy, especially alkylating agents, is also carcinogenic, although more likely to induce leukemia than a solid tumor, and within a much shorter latency period. The addition of chemotherapy during RT also increases the risk. Some of the best data come from follow-up of childhood survivors,⁷⁰ although also identifying large variations in findings. In children, susceptibility varies according to age and the type of tissue irradiated, with leukemia developing after 5–8 years, and solid tumors, the commonest of which are thyroid cancers, breast cancers, and bone and central nervous system malignancies, usually occurring many years later.^{71,72} Some second primary malignancies, especially carcinomas, arise around the periphery of the high-dose volume. Concerns have been expressed about the risk of techniques such as IMRT: although they have very conformal high-dose

volumes and can minimize dose to critical structures, there is a large lower-dose volume from the multiple-beam entry through normal tissues.^{71,73} Thyroid cancer is unlikely when the gland has received doses over 30 Gy. Conversely, sarcomas tend to arise in heavily irradiated tissues, and appear to have a dose–response effect. Survivors of Hodgkin's disease treated with mantle radiation (i.e., mediastinal, cervical, and axillary nodal XRT with shields over the lungs) have four times the risk of developing breast cancer. The woman's age at the time of XRT is extremely important: adolescent girls aged 10–16 years have a 136-fold greater risk of developing breast cancer than their nonirradiated peers.⁷⁴ Factors such as smoking can markedly increase the risk of developing primary lung cancer, even in parts of the lung that received only a tiny scattered dose. Some genetic predispositions, such as Li–Fraumeni syndrome, which is linked to germline mutations of the p53 suppressor gene, or ATM and RB gene carriers, are exquisitely susceptible to any form of radiation.

Exposure to radiation

Radiation accident studies have shown that there is a proportional relationship between the amount of radiation exposure and the risk of developing cancer.⁷⁵ The sievert (Sv) is the SI unit that measures the biological effect of absorbed dose, taking into consideration the relative biological effectiveness of the radiation (e.g., 1 for photons and electrons, 20 for high-dose neutrons and α -particles) and the biological effect on different organs. When all of these weightings are 1, then 1 Sv = 1 Gy. The gray is a unit of absorbed dose in any material defined only by physical, not biological, properties of radiation. The sievert is used to quantify risk of radiation damage, including cancer. To put this into perspective, on average, a chest X-ray is 0.34 mSv, mammogram 0.48 mSv, and CT thorax 6 mSv. The biggest contributor of background radiation source is radon, which is approximately 2 mSv annually. There is background cosmic radiation of 0.24 mSv per year, and a passenger on a return flight between Seattle, WA and Toronto, ON would be exposed to 0.085 mSv. Radiation oncologists are limited to an occupational exposure of 50 mSv per year, excluding medical and background sources of radiation, but after the March 2011 earthquake and subsequent explosion in a nuclear reactor, the emergency nuclear workers at Fukushima, Japan were exposed to up to 400 mSv per hour. The Japanese public already has a 20–25% lifetime risk of cancer, and exposure to 400 mSv increases that risk by 2–4%. Survivors of the atom bombs in Hiroshima and Nagasaki have an excess risk of cancer (RR 1.42 at 1 Sv) that persists through their lifetime. Exposure to 1 Sv increases the lifetime risk of fatal cancer by approximately 5%. The most sensitive organs to this sort of accidental exposure are bone marrow and thyroid, and leukemia is the most common resulting malignancy. Radiation sickness is an acute effect of radiation exposure, causing nausea, headache, and bone marrow suppression, and is rarely experienced at exposures of less than 1 Sv.

Regardless of the regulatory safety requirements, the ALARA (As Low As Reasonably Achievable) principle is the mantra of all who work with ionizing radiation in their efforts to reduce the risk of harm. Ways to minimize radiation exposure include reducing time of exposure, increasing the distance from the radiation source, and utilizing adequate shielding.

Conclusion and future trends

Radiation treatment uses ionizing radiation to treat malignancies as a primary therapy, or, more importantly now, as part of a planned collaborative multidisciplinary approach, used in combination with systemic therapy and surgery. Like surgery, it is a local therapy, and has a curative, adjuvant, or palliative role in managing most cancers. Although acute toxicities are reversible, late toxicities are not, and are related mostly to the loss of normal fibrosis mechanisms. The risk of radiation-induced malignancy, as well as other late side effects, becomes more important as more cancers are cured, and the proportion of survivors grows.

Dramatic advances in radiation treatment planning, delivery, and verification technology have increased the accuracy and precision of treatment, allowing higher doses to tumor,

and reducing the risk of radiation injury by sparing more normal tissue. Improvements in RT-planning systems provide not only the ability to apply dose constraints to specified structures, but also to provide data that help quantify risk of toxicity, in tandem with better reporting and collection of data and outcomes. These approaches all contribute to improving the prevention of radiation injury. Radioprotection also occurs by reducing risk of radiation damage through modification of delivery techniques, but modulating radiation cellular response is of greater importance. Although this concept has been studied for years, clinical results have been disappointing; nevertheless, a new generation of biological modifiers offers greater hope. However, the future of radiation oncology lies in biology, and specifically bioengineering and tissue regeneration, and the imperative to repair the damage that has already been caused.



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Pathophysiology of lymphedema

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SYNOPSIS

- Lymphedema is a progressive disease that can occur as a result of congenital defects, iatrogenic injury, or infection of the lymphatic system.
- The lymphatic system is comprised of capillary lymphatics that drain into progressively larger collecting vessels.
- The pathology of lymphedema is due to accumulation of lymphatic fluid leading to chronic inflammation, fibrosis, and adipose deposition.
- Obesity and radiation significantly increase the risk of lymphedema after surgery.

Introduction

Lymphedema is a progressive disease of the lymphatic system characterized by chronic inflammation, adipose deposition, hyperkeratosis, and fibrosis. Although the precise mechanisms regulating the development of lymphedema remain unknown, a key inciting event is lymphatic dysfunction and impaired clearance of interstitial fluids. As a result, lymphedema can develop due to genetic/developmental abnormalities of the lymphatic system (i.e. primary lymphedema) in which lymphatic vessels are absent or poorly developed. Primary lymphedema may also occur secondary to pathologic processes that directly impair lymphatic function. More commonly, lymphedema develops after trauma or infection of the lymphatic system (secondary lymphedema). These inciting events set off a cascade of tissue changes that in some cases ultimately results in massive accumulation of adipose tissue and the classic findings of elephantiasis (Fig. 27.1).

Estimates of the incidence of lymphedema vary widely. Some studies report as many as 200 million patients in developing countries who suffer from lymphedema secondary to parasitic infections by *Wuchereria bancrofti*. This disease has a variable course with smoldering disease in some and rapidly progressive/disabling lymphedema in others. Case reports of

massive extremity or scrotal lymphedema in patients with filariasis have been reported resulting in significant morbidity and mortality.

In the United States and Europe, the most common cause of lymphedema is cancer treatment. Breast cancer survivors comprise the largest group of affected individuals due to the high incidence of breast cancer in these regions. It is estimated that as many as 30–60% of breast cancer patients treated with axillary lymph node dissection go on to develop lymphedema.^{1,2} Recent advances in sentinel lymph node biopsy have decreased the requirement for full axillary lymph node dissection and have decreased the incidence of lymphedema. However, lymphedema does develop even after sentinel lymph node biopsy in 5–7% of patients.^{3,4} Lymphedema is not exclusively a disease of breast cancer survivors and occurs as a complication of treatment of most other solid tumors, most commonly gynecological cancers, melanoma, pelvic tumors, and sarcomas. In fact, a recent meta-analysis estimated that nearly 1 in 6 patients treated for a variety of solid tumors go on to develop lymphedema.^{5,6} The development of lymphedema in patients with sarcomas is an interesting phenomenon since lymph nodes are rarely removed in these tumors, suggesting that widespread injury to the superficial lymphatic system (as would occur with a wide excision of a skin sarcoma in combination with radiation therapy) can sufficiently disrupt the lymphatic vasculature and lead to the development of lymphedema even when the regional lymph nodes are not injured.

Anatomy and physiology

Lymphatic circulation

The lymphatic system plays a key role in a number of physiologic processes including interstitial fluid and immune cell transport, regulation of inflammation, responses to host or foreign antigens, and fat absorption, among others. The

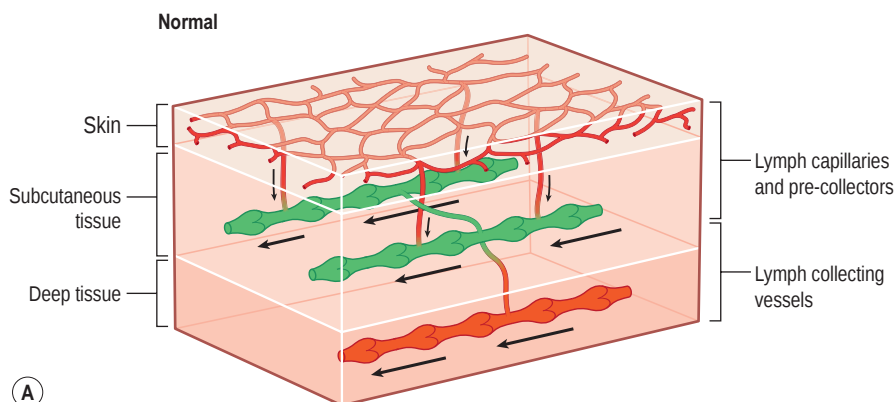
transport of immune cells and interstitial fluid from the periphery begins in capillary lymphatics located in the dermis (Fig. 27.2). These vessels are comprised of a single layer of lymphatic endothelial cells (LECs) that are physically tethered to the surrounding tissues by anchoring filaments and to each

other by overlapping or intercalating button-like junctions. Minute changes in tissue fluid content causes adjacent LECs to separate due to the physical connections of these cells with the surrounding tissues by anchoring filaments, thus enabling entrance of cells and interstitial fluid into the initial lymphatics. Once the interstitial fluid has entered the lymphatic system, the overlapping regions between LECs is re-established maintaining the fluid within the lymphatic vessel. Fluid is propelled passively to pre-collectors and collecting lymphatics located in the deeper dermis and subcutaneous tissues. The LECs in collecting vessels, in contrast to the capillary lymphatics, have continuous endothelial cell junctions that prevent fluid leak with physical changes in the microenvironment. In addition, collecting lymphatics have a basement membrane and are covered by smooth muscle cells that can contract to propel lymphatic fluid forward. Lymphatic collectors also have bicuspid valves located every 1–2 mm that ensure one-way flow of interstitial fluid blocking backflow into the capillary lymphatic system. The functional lymphatic unit is defined as a lymphangion and contains a region of collecting lymphatic vessel between two valves (Fig. 27.3).

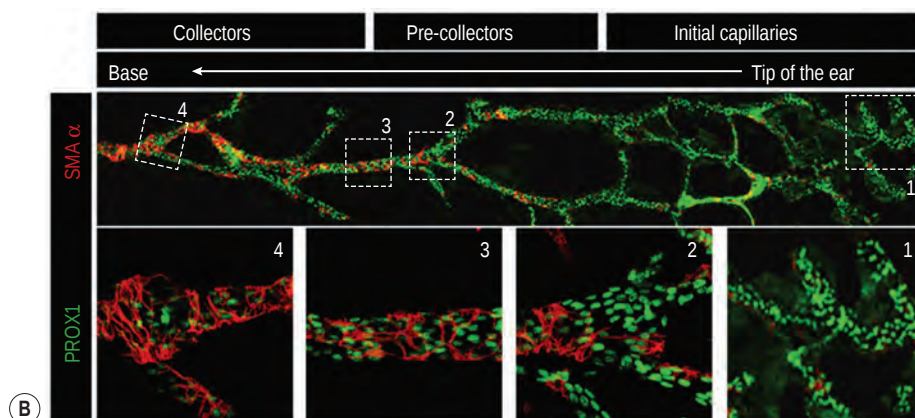
Lymphatic flow is determined by two factors. Passive compressive forces arise from external compressive forces such as muscle contractions, respiration, regional arterial pulsation, and gravity. These forces, as their name implies, passively propel interstitial fluid centrally. In normal limbs (i.e. without history of lymphatic injury), passive compressive forces such as massage or muscular contractions do not significantly increase lymphatic pressure in collecting lymphatics and do not increase flow. Active compressive forces arise from



Fig. 27.1 Severe (grade III) lymphedema of the left leg after melanoma resection.



(A)



(B)

Fig. 27.2 Microscopic anatomy of the lymphatic system. (A) Schematic of superficial and deep lymphatics of the skin. (B) Fluorescent immunohistological depiction of mouse ear skin lymphatic tree. Mouse ear skin whole mount stained for Prox1 (pan LEC marker) and Smooth muscle actin alpha to identify the capillary, pre-collecting and collecting lymphatic vessels in a single plane (upper panel). High magnification images 1, 2, 3 and 4 from the upper panel image showing spatial separation of capillaries at the ear tips to collectors at ear base. Note the collecting lymphatic vessels being tightly wrapped by SMA cells enabling them to pump the lymph. (A, Adapted from Suami H, Pan WR, Taylor GI. Changes in the lymph structure of the upper limb after axillary dissection: radiographic and anatomical study in a human cadaver. *Plast Reconstr Surg.* 2007;120:982–991.)

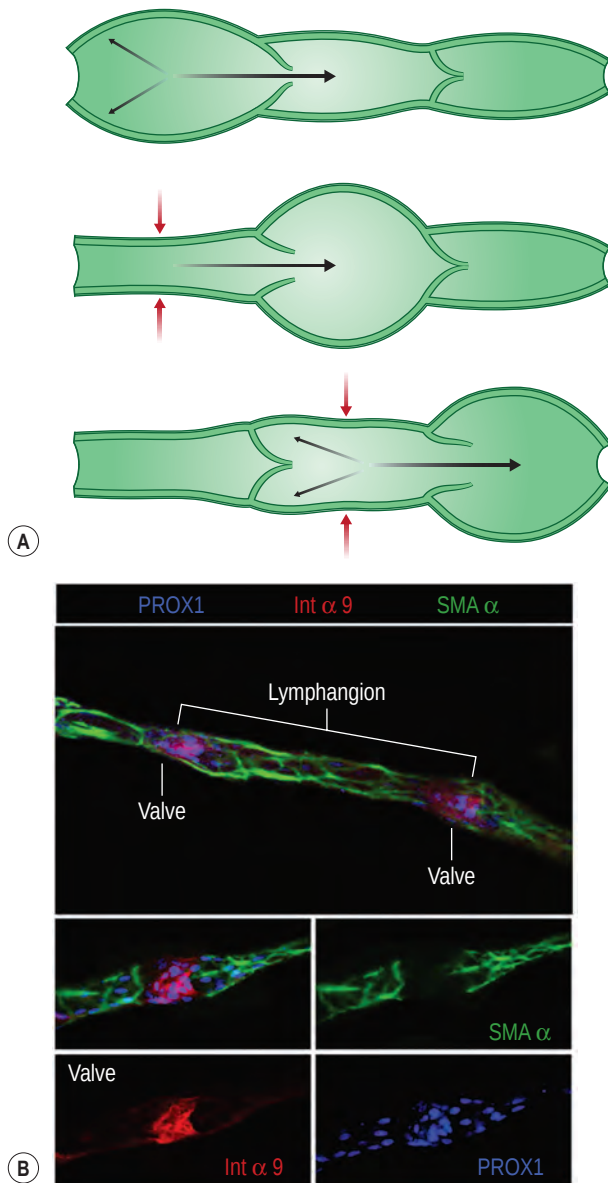


Fig. 27.3 Anatomy of a lymphangion. (A) Schematic representation of a lymphangion (segment of lymphatic collector between two valves). (B) Fluorescent immunohistological representation of a lymphangion (segment of lymphatic collector between two valves) in mouse ear skin (upper). Note the 2 valves immunopositive for integrin alpha 9 (a valve marker). High magnification image of a single valve showing SMA cells (green), valve leaflets (red) and PROX1 stained LECs (blue).

intrinsic contraction of smooth muscle cells surrounding the collecting lymphatics. These muscle cells are unique in that they have features of both smooth and striated muscles and have basal myogenic activity. Myogenic forces in the lymphatic system, similar to the heart, are responsive to preload and afterload pressure changes. In addition, the force and frequency of lymphatic pump contraction can be modulated by vasoactive substances such as histamine and substance P, among others. In general, increases in preload and after load lead to an increase in contraction frequency and strength up to a point. Persistent increases beyond this point lead to lymphatic pump failure and vessel dilatation.

Lymph nodes

Lymph nodes filter lymphatic fluid as it is transported within the lymphatic system back to the venous circulation (Fig. 27.4). Although the number of lymph nodes is somewhat variable, a typical adult has 600–700 lymph nodes located in various regions and clustered in areas where body parts come together or in/around intra-abdominal organs. Interstitial fluid is transported centrally by collecting lymphatics and enters the subcapsular sinus of the lymph node via afferent lymphatics. From there, the interstitial fluid (and the antigens, antigen-presenting cells, and inflammatory cells it contains) drain through lymph sinuses that surround lymph node follicles where B cells reside. Lymphatic sinuses are lined by reticular endothelial cells and antigen-presenting cells enabling presentation and response to self/foreign antigens. Macrophages located in these regions can also phagocytose bacteria for processing and clearance. In addition, fluid exchange occurs through regional high endothelial venules that permeate the lymph node enabling hematogenous delivery of immune cells and cytokines to the lymph node. The lymphatic fluid exits the lymph node via efferent lymphatics located at the lymph node medulla progressing to the next lymph node chain or centrally for return back to the venous system.

Etiology of lymphedema

Primary lymphedema

Numerous genetic defects are associated with development of primary lymphedema (Table 27.1). These disorders have a highly variable natural history in terms of timing of presentation and severity of symptoms. In addition, primary lymphedema may be familial with known or suspected genetic defects, may occur as a result of spontaneous mutations, or in some cases develop without a known cause. Familial forms of primary lymphedema, even within members of the same family, can have different presentation due to the penetrance of the genetic mutation or causative factors and interaction with environmental regulators. Thus, in some cases primary lymphedema may present shortly after birth (i.e. congenital lymphedema) or, more commonly, become manifest years later with progressive symptoms (lymphedema praecox or lymphedema tarda).

In most cases of primary lymphedema, the lymphatic system is poorly developed with decreased numbers of lymphatic vessels (most commonly collecting lymphatics). It is unclear if patients with primary lymphedema have defects of the lymphatic system at birth or if these changes develop postnatally. The current evidence suggests that in most cases some degree of lymphatic dysfunction is present at birth and that these changes gradually worsen over time. The rate at which these changes occur is variable and can be altered by environmental factors leading to differential presentation of the disease. Studying these changes has been a challenge due to our inability to serially monitor the lymphatic system non-invasively; however, recent advances with lymphatic imaging have been helpful in this regard.

Congenital lymphedemas occur more commonly in females, more commonly involve the lower extremities, and account

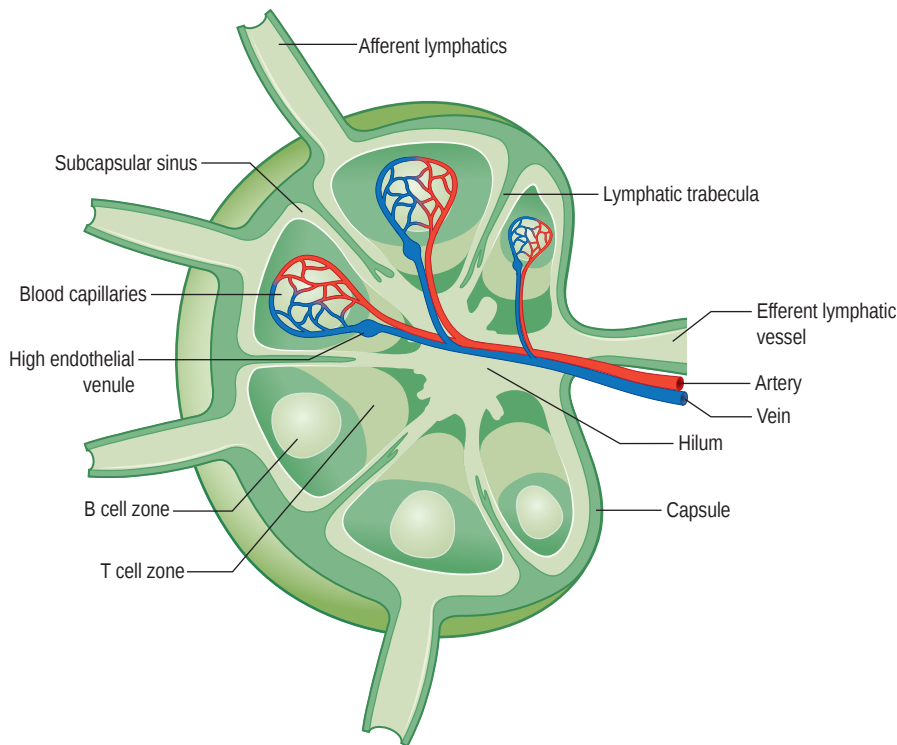


Fig. 27.4 Schematic figure of a lymph node. Lymph enters the lymph node subcapsular sinus via afferent lymphatics and drains through the node via lymph sinuses, eventually exiting the node via the efferent lymphatics in the hilum. Blood capillaries and high endothelial venules enable leukocytes to enter the lymph node and are a site of fluid exchange.

Table 27.1 Genetic mutations and lymphedema

Gene	Syndrome	Pathology	References
<i>FLT4</i> (5q35) (coding region for <i>vascular endothelial growth factor receptor 3</i>)	Milroy disease	Primary lymphedema of the lower extremities. Upslanting “ski jump” toenails due to nail bed edema	64, 65, 81
<i>FLT4</i> (4q34) (coding region for <i>vascular endothelial growth factor C</i>)	Milroy-like lymphedema	Congenital lower limb lymphedema	73
<i>FOXC2</i>	Lymphedema-distichiasis syndrome	Lower-limb lymphedema most often presents at puberty; double row of eyelashes	72, 73, 82
<i>SOX18</i>	Lypotrichosis–lymphedema–telangiectasia syndrome	Lymphedema, hair loss, and small dilated blood vessels near the surface of skin	74
<i>GJC2</i> (coding for <i>connexin 47 (CX47)</i>)	Meige’s disease	Impaired gap junction activity, increased risk of breast cancer-related lymphedema	7
<i>CCBE1</i> (18q21) (encodes for <i>collagen & calcium binding EGF domain 1</i>)	Hennekam syndrome	Severe lymphedema in limbs, genitalia, and face; facial anomalies; seizures, mental retardation; and stunted growth. Symptoms often present <i>in utero</i>	75
<i>KIF11</i> (10q24)	MCLMR syndrome	Microcephaly, congenital lower limb LE, ocular abnormalities, learning disabilities	76
<i>GATA2</i> (3q21)	Emberger syndrome	Unilateral or bilateral lower limb lymphedema; presents in childhood; severe cutaneous warts; myelodysplasia	77
	WILD syndrome	WILD syndrome (warts, immunodeficiency, lymphedema, and dysplasia)	78
<i>AKT1</i>	Proteus syndrome	Lymphatic malformations, skeletal, cutaneous, and CNS abnormalities	79,80

for 10–25% of all primary lymphedemas.⁷ The degree of swelling of the limbs can be variable and in some cases may result in severe abnormalities in one limb and relatively mild or absent disease in the contralateral limb. Milroy's disease is a familial, sex-linked disorder in which inactivating mutations occur in the vascular growth factor receptor-3 (VEGF-R3). These mutations account for a relatively small number of patients with primary lymphedema (2–3%) and usually present shortly after birth with limb swelling and/or chylothorax. The pathophysiology of this disease arises from the fact that VEGF-R3 is primarily expressed by lymphatic endothelial cells and serves as a key signaling molecule for endothelial growth factor C (VEGF-C) and its closely related molecule VEGF-D. Activation of VEGF-R3 results in transmission of intracellular signals that regulate lymphatic endothelial cell differentiation, proliferation, migration, and endothelial-derived nitric oxide production. Not surprisingly, patients with Milroy's disease have hypoplastic lymphatic vessels with variable severity of dermal and collecting lymphatic vessel agenesis.

In contrast to congenital lymphedemas in which the disease presents shortly after birth, patients diagnosed with *lymphedema praecox* present with lymphedema at some point before the age of 35. The vast majority of these patients develop unilateral lower extremity lymphedema and the disease has a 4:1 female to male ratio. Additional evidence implicating a sex-hormone link with this disease is the fact that most patients begin to become symptomatic at the time of puberty.⁷ Histologic examination of patients with lymphedema praecox has shown variable pathologic findings; however, these patients often exhibit fewer capillary lymphatics and hypoplastic collecting vessels. Most patients present with unilateral lower extremity lymphedema (~70%) at some point between birth and age 35. These patients characteristically have decreased number and caliber of lymphatics and most commonly present during puberty with a female to male ratio of 4:1.

The diagnosis of *lymphedema tarda* refers to patients who develop primary lymphedema after the age of 35. This disease is a diagnosis of exclusion since secondary causes of lymphedema are much more common in this age group. In addition, lymphedema tarda is an infrequent presentation of primary lymphedema and occurs most commonly in the lower extremities of women. Although the pathophysiology of this disease remains largely unknown, recent studies have shown an association with loss-of-function mutations in the *FOXC2* gene.^{8–10}

The validity of classification schemes that categorize primary lymphedema based on the age at which symptoms present has been recently debated. This debate centers on the fact that presentation of these disorders is highly variable due to genetic and environmental factors and that this variability decreases the utility of these categories for diagnosis. As a result, recent studies have attempted to develop new classification schemes based on the presentation of disease and known genetic mutations.¹¹ This approach categorizes congenital lymphedemas into five main groups: syndromic, systemic or visceral, disturbed growth, congenital onset, and late onset. The developers of this system contend that this diagnosis algorithm is more precise and as a result can be useful for developing and testing of diagnostic or therapeutic interventions.

Secondary lymphedema

Secondary lymphedemas develop after injury or obstruction of the lymphatic system. For example, infections with parasites in filariasis results in chronic obstruction of lymphatic channels and subsequent immune responses that impair lymphatic function leading to progressive disease.¹² Filariasis is caused by roundworms (most commonly *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori*) that are transmitted by mosquitos. The adult worms grow in the tissues and release larvae into the blood stream (microfilariae) that are diagnostic for the disease. However, patients with clinical disease may be free of microfilariae in the blood, in which case the diagnosis is made either clinically, or by tissue biopsies, or serum antigen testing. Filariasis is a major cause of morbidity in developing countries and treatment remains limited to anti-parasitic medications that only kill the developing larvae rather than the adult worm.

Iatrogenic lymphatic injury in the course of cancer treatment is another major cause of secondary lymphedema. In fact, lymphedema is the most common long-term complication of cancer treatment (even more common than radiation-induced sarcomas, or chemotherapy-induced renal or cardiac failure). Lymphedema can develop in the course of treatment for virtually all solid tumors including breast, gynecological tumors, melanoma, sarcoma, and pelvic tumors. Lymphedema can even develop after extirpation of head and neck tumors (4% incidence) resulting in cosmetic deformity and functional compromise.

Secondary lymphedema in cancer survivors occurs most frequently months and sometimes years after the initial surgery (Fig. 27.5). This delayed presentation together with the fact that lymphedema develops in only a subset of patients who undergo lymphadenectomy is important since these findings suggest that lymphatic injury is necessary but not sufficient for the development of the disease. Thus, additional pathological changes are needed for patients to develop lymphedema after lymph node dissection.

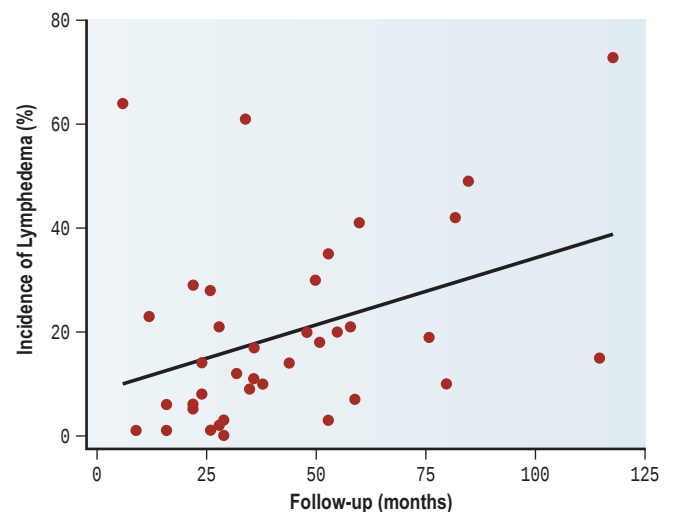


Fig. 27.5 Timing of lymphedema (linear prediction) presented as a scatterplot of median follow-up times of various studies. Note that development of lymphedema occurs in a delayed fashion after surgery. (From Cormier, et al. *Lymphedema beyond breast cancer: a systematic review and meta-analysis of cancer-related secondary lymphedema*. Cancer. 2010;116:5138–5149.)

On average, secondary lymphedema in breast cancer survivors develops approximately 8 months after the initial surgery.¹³ In addition, the majority of patients (75%) are diagnosed within the first 3 years.² In one unusual case report, a patient developed lymphedema after a seemingly innocuous injury 50 years after the initial lymphatic injury. Thus, in most cases the acute surgical swelling that develops after breast surgery and lymphadenectomy resolves within the first few weeks of surgery and, in most cases, never recurs. However, in some patients it recurs in a progressive and permanent manner 8–12 months later. This process appears to be accelerated somewhat in the lower extremity (perhaps due to the effect of gravity) with lymphedema developing on average 4–6 months after surgery.

Once lymphedema develops, it is usually progressive in nature with disease worsening over time. Although the rate of disease progression can be decreased with aggressive physical therapy and early diagnosis of lymphedema, some unfortunate patients progress rapidly even despite wrapping and aggressive symptomatic treatment. In addition, the rate of disease progression in patients with lymphedema in general is highly variable with some patients experiencing relatively indolent disease necessitating little to no compression while others progress rapidly to disabling disease that has little response to therapy.¹⁴ Although the efficacy of manual lymphatic massage has been debated, most studies suggest that these treatments are helpful in most patients, resulting in decreased symptomatology and diminished rate of progression. In addition, these interventions are most effective in early stage disease, therefore careful follow-up of patients who are at risk for disease has been advocated.

The rate of disease progression and severity of disease can be modulated by exercise and weight-loss programs. These interventions are effective in both prevention and treatment of lymphedema and should be encouraged in all at-risk individuals.^{15,16} Interestingly, for many years physicians and therapists warned patients who had undergone lymph node dissection to avoid strenuous exercise or weight lifting with their affected limb based on an idea that these activities would increase blood flow to the limb and in turn increase lymphatic load.² However, this myth was eventually disproven by a number of prospective randomized control studies demonstrating efficacy of weight loss and exercise in the treatment of lymphedema.^{17,18}

Diagnosis

The diagnosis of lymphedema is usually made by clinical exam and, in some cases, radiologic tests. The differential diagnosis of primary or secondary lymphedema includes venous insufficiency, congestive heart failure, malignancy (either recurrent or primary causing lymphatic obstruction), and infections. Patients with lymphedema often present with swelling, skin tightness, heaviness, and fatigue. More rarely, the presenting symptom is cellulitis and rapid swelling of the affected extremity. Limb circumference and volume measures are useful means of analyzing the degree of swelling in unilateral cases and these measures are commonly used as a means of following disease progression (Fig. 27.6). Differences of more than 2 cm or a volume differential of more than 200 cc is considered by most sources diagnostic of lymphedema,



Fig. 27.6 Lymphedema measurements. (A) Circumference measurements for upper extremity lymphedema. (B) Water displacement method for calculating limb volume. (Adapted from Pitsch F. Benefit of dalfon 500 mg in chronic venous disease related edema. *Phlebology*. 2006;13:17–21.)

with some schemes classifying patients based on measured differences.¹⁹ The use of measurements alone can be problematic in some cases due to the relative subjective nature of this test (i.e. a 2 cm difference in a thin patient is likely much more significant than a 2 cm difference in a morbidly obese individual). Nevertheless, measurements are a cornerstone of lymphedema diagnosis and treatment.

Circumference measurements are usually performed at defined intervals (in many cases 5 cm below and 5 cm above the olecranon); however, a wide range of measures have been reported. In addition, the inter and intra-operator validity of circumference measurements has been questioned although several reports have provided evidence that with training these measurements can be performed reproducibly. Limb volume measurements can be performed with water displacement; however, this approach can be difficult for practical purposes (for example some hospitals require using sterile fluid for each patient). The perometer is an infrared scanner that measures the limb circumference (arm or leg) in multiple areas and then uses the truncated cone formula to calculate limb volume and volume differentials (Fig. 27.7).^{20,21} This device is useful but is unfortunately expensive and not widely available in the United States. Limb volumes can also be calculated by measuring limb circumferences at 4 cm intervals and using the truncated cone formula as described by Brorson.²² This approach is simple to perform and is a good compromise between water displacement/perometer and limb circumference measurements.

Radiologic tests can be useful in the diagnosis of lymphedema. For example, lymphoscintigraphy is a procedure in which a radiolabelled colloid is injected in the distal extremity

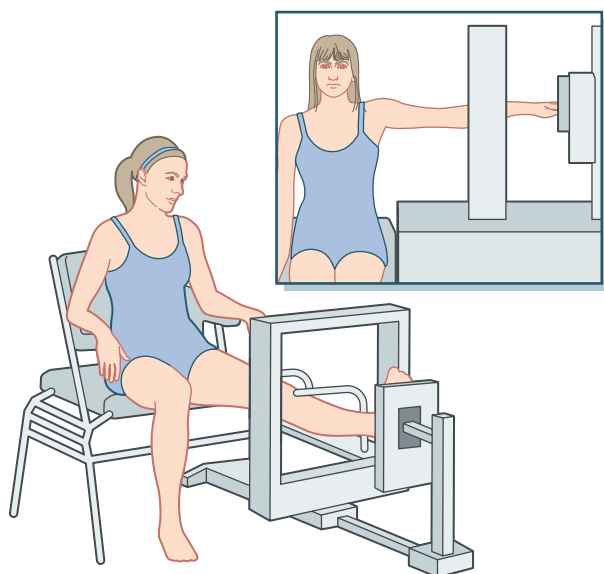


Fig. 27.7 Lower limb (left) and upper limb (right) perometer measurements. (Adapted from Pero-systems Inc.)

and the rate/amount of uptake is then analyzed in the draining lymph node basins.^{23,24} Lymphoscintigraphy can also be used to estimate dermal backflow, a condition in which lymphatic blockage proximally results in the redirection of lymphatic fluid from deep channels into the superficial lymphatics. However, recent reports have suggested that the sensitivity of lymphoscintigraphy (0.61) for early stage lymphedema is lower than other methods such as MRI and indocyanine green (ICG) lymphangiography.²⁵ The lymphatic vessels and pathologic changes in lymphedema can also be visualized using MRI (MRI lymphangiography) with a high degree of sensitivity and specificity.^{25–27} However, this technique is user- and radiologist-dependent and requires optimization of techniques.

Recent studies have advocated the use of indocyanine green (ICG) near-infrared (NIR) lymphangiography in the diagnosis and staging of lymphedema. In this test, ICG dye is injected in the dermis of the affected extremity and lymphatic vessels are visualized using a NIR camera. It is important to note that the use of ICG is currently only FDA approved for intravenous injection and that intradermal injections for visualization of the lymphatic system are an off-label use. This method enables visualization of the superficial collecting lymphatics, dermal backflow, and abnormal lymphatic vasculature and is a helpful adjunct to the diagnosis of lymphedema. Recent reports have suggested that ICG lymphangiography has a high degree of sensitivity and specificity for diagnosing lymphedema and that pathologic changes such as splash/stardust/diffuse patterns are present even in early-stage disease (Fig. 27.8).²⁵ In fact, some authors have developed lymphedema staging systems based on ICG lymphangiography (see below).²⁸ Experimental reports have also shown that lymphatic pumping capacity (the rate of change in fluorescence intensity in a given vessel over time) can be a useful measure of lymphatic function; however, this analysis has not been widely adopted.

A few non-invasive methods are available for the diagnosis of lymphedema. For example, with bioimpedance, the rate of

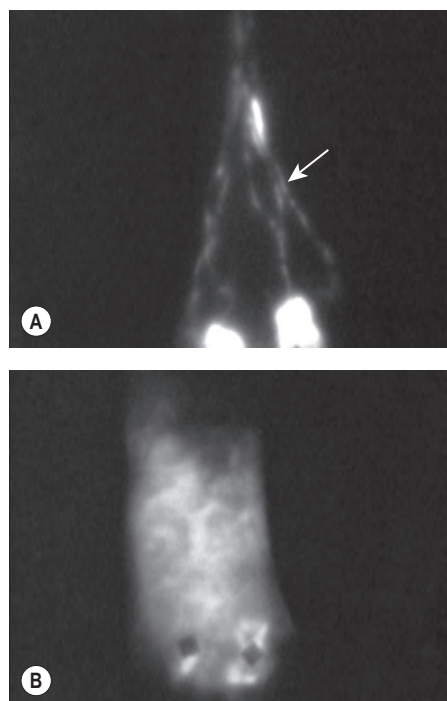


Fig. 27.8 ICG anatomy of normal and lymphedematous limbs. (A) Collecting vessels are clearly identified in the normal dorsal hand (arrow points to injection site). (B) Lymphedematous hand with extensive dermal reflux and lack of clearly identifiable lymphatics.

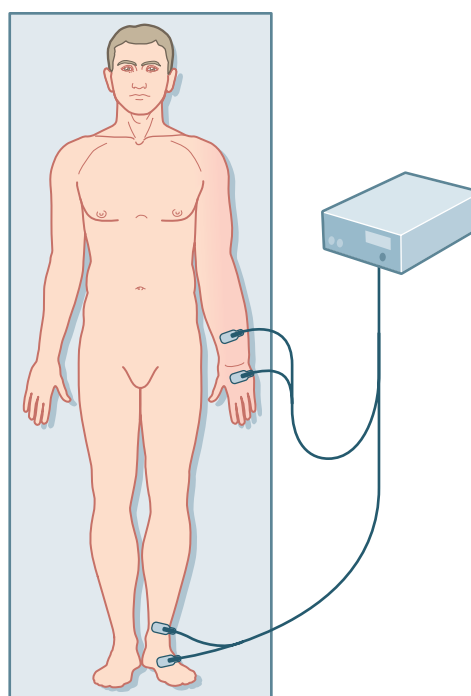


Fig. 27.9 Bioimpedance measurement compares the rate of electrical transmission between the lymphedematous and normal limbs.

electrical current transmission through tissues, is used to estimate the fluid content of the lymphedematous limb as compared with the normal limb (Fig. 27.9).²⁹ Although this test can have variable results due to skin temperature, superficial skin dryness, and other factors, some studies

have suggested that bioimpedance is helpful in the diagnosis of early-stage lymphedema in which volumetric or circumference differences are subtle or non-existent. Finally, the degree of skin and soft tissue fibrosis can be estimated with a tonometer and followed longitudinally to monitor disease progression.^{30,31}

Lymphedema classification

Common classification systems for lymphedema rely primarily on the clinical features of the disease. The International Society of Lymphology staging system is the most widely used scheme and is based on measurable swelling and presence or absence of pitting (Fig. 27.10; Table 27.2).³² In this scheme, patients who have a history of lymphatic injury and present with symptoms of lymphedema (e.g. heaviness, fatigue) without swelling or measurable volume changes are classified as latent lymphedema (stage 0). Patients with stage I lymphedema (also known as spontaneously reversible lymphedema) have measurable swelling and pitting edema that improves with elevation or use of compression garments. Stage II lymphedema (spontaneously irreversible lymphedema) is characterized by accumulation of fibroadipose tissues that prevents reversal of symptoms by elevation or compression. Finally, patients with severe swelling, fibrosis, hyperkeratosis, and end-stage lymphedema symptoms are diagnosed with stage III or lymphostatic elephantiasis.³³

Changes in limb circumference or volume as compared to the contralateral limb or preoperative values have also been used as a means of classifying the severity of lymphedema.^{19,34} Although there is variability in these studies, the majority of reports classify patients with limb circumference excess of 2 cm or 100 cc volume differential as mild lymphedema. Differences of 2–4 cm (or more than 200 cc volume) is considered moderate lymphedema. Patients who have measured differences of 4 cm or more are classified as having severe lymphedema. The utility of this classification scheme, however,

Stage	Pathophysiology	Description
0	Latent lymphedema	Lymphatic vessels are injured. Capacity for fluid transport is impaired, but still sufficient to drain lymph as necessary. Lymphedema has not yet occurred or is not yet apparent.
I	Spontaneously reversible lymphedema	Pitting has started – the affected area indents when pressure is applied to it. Swelling can be contained with the use of compression garments.
II	Spontaneously irreversible lymphedema	Affected tissue is considered to be non-pitting and has a spongy consistency. Fibrosis starts to occur as the limbs harden and increase in size. At this point, compression garments are ineffective at suppressing symptoms.
III	Lymphostatic elephantiasis	Swelling is irreversible, and the tissue is heavily fibrosed and unresponsive to treatment. Skin has become significantly thickened.

is highlighted by the fact that it assumes that the limbs had equal circumference or volume preoperatively (a false assumption in many patients due to differences based on hand/leg dominance). In addition, not taking into account a patient's body habitus is problematic since a 2 cm difference is much more significant in a thin patient than in an obese patient.

ICG lymphangiography has been proposed by some researchers as a useful means of classifying patients with lymphedema. These efforts are important since they attempt to use physiologic changes in addition to clinical exam findings. Koshima *et al.* have proposed a system based on their experience with lymphovenous bypass procedures (Table 27.3). These authors classified the progression of secondary lymphedema into 4 steps based on ICG findings and termed this scheme the NECST system (Fig. 27.11).²⁸ The initial step in the disease process is normal lymphatic vessels distal to the zone of lymphatic injury. This is followed by lymphatic ectasis (dilated lymphatics with flattening of lymphatic endothelial cells), followed by contraction (loss of intraluminal diameter in collecting lymphatics and thickening of smooth muscle cell covering), and finally sclerosis (obliteration of the lumen with proliferative smooth muscle cells).

The M.D. Anderson classification scheme also classifies lymphedema into four stages based on ICG findings and quantification of dermal backflow (Fig. 27.12; Table 27.4).³⁵ In this scheme, stage 1 patients have numerous patent lymphatics and minimal/no dermal backflow. Stage 2 patients have a moderate number of lymphatics and segmental dermal backflow. Stage 3 patients have few patent lymphatics with significant dermal backflow throughout the entire arm. Finally, stage 4 patients have no patent lymphatics and severe dermal



Fig. 27.10 Patient with pitting edema of the upper extremity resulting from breast cancer-related lymphedema.

Table 27.3 Koshima lymphedema staging system

Type	Description
Normal type (Step 0)	Lymphatic vessels are normal and fully functional
Ectasis type (Step 1)	Endolymphatic pressure is noticeably increased, causing lymphatic endothelial cells to flatten. Lymphangiectasia, the dilation of lymphatic vessels, starts to occur
Contraction type (Step 2)	Smooth muscle cells are converted into synthetic cells, promoting collagenous fiber growth. The wall of the lymphatic vessel starts to thicken
Sclerosis type (Step 3)	Lumen of lymphatic vessels are narrowed if not completely obstructed. Most of the tissue is fibrosed, and lymphatic vessels have lost their ability to transport and concentrate lymphatic fluid

(Data from Mihara M, Hara H, Hayashi Y, et al. Pathological steps of cancer-related lymphedema: histological changes in the collecting lymphatic vessels after lymphadenectomy. *PLoS One*. 2012;7:e41126.)

Table 27.4 M.D. Anderson ICG lymphedema classification system.³⁵

Stage	Description
1	Many patent lymphatic vessels present and minimal dermal backflow can be observed in localized areas
2	Moderate number of lymphatic vessels can be seen with segmental dermal backflow
3	Few patent lymphatic vessels can be seen and significant dermal backflow can be observed throughout the entire arm
4	No patent lymphatic vessels can be seen. Severe dermal backflow throughout the entire arm and hand is apparent

backflow of the entire arm and hand. Although this scheme is somewhat subjective, the authors have found that it is useful for classification and patient selection for lymphovenous bypass procedures.

Pathophysiology of lymphedema

Although lymphedema is common and morbid, surprisingly little is known about the pathophysiology of this disease. The histological hallmarks of the disease are edema, fibroadipose tissue deposition, chronic inflammation, and hyperkeratosis and recent studies have begun to shed light on how lymphatic injury leads to these protean symptoms (Fig. 27.13). A key concept in understanding the pathology of lymphedema is that lymphatic injury is only the initiating step and that additional pathological events are necessary for the development of lymphedema clinically. This concept is highlighted by the fact that lymphedema only develops in a subset of

patients who undergo lymphadenectomy, and even in these individuals does so in a delayed fashion usually months to years after surgery. A better understanding of these pathological events is necessary for improved diagnosis and development of rational targeted treatment or prevention options. Although a number of studies have analyzed lymphatic vascular changes in primary lymphedema and have identified a wide variety of defects, the remainder of this discussion will be dedicated to pathophysiological changes that occur in secondary lymphedema following cancer therapy.

Lymphatic vascular defects in secondary lymphedema

Lymphangiographic studies performed acutely after axillary lymph node biopsy (i.e. before onset of lymphedema) demonstrate dilated collecting lymphatics and blockage of flow in these vessels in the axilla. Patients at this stage have subclinical interstitial fluid stasis that is either not clinically measurable (stage 0 or latent lymphedema) or resolves spontaneously with compression/elevation (stage I). Persistent subclinical interstitial fluid stasis results in further dilatation of the collecting lymphatics, lymphatic valvular incompetence, and retrograde flow to capillary lymphatics located in the superficial dermis (i.e. dermal backflow). At this point, the collecting lymphatics maintain the ability to actively contract, however the pulsations become more irregular with loss of correlation between lymphatic pulse amplitude and stroke volume.³⁶ Lymphatic stasis leads to activation of endogenous danger signals by local cells (adipocytes, endothelial cells, myocytes, and inflammatory cells) which in turn promote activation of chronic inflammatory pathways, expression of inflammatory cytokines, and further promotion of leukocyte entry into the lymphedematous tissues.³⁷

In the early stages of injury following lymph node dissection, chronic inflammation and subclinical lymphatic fluid stasis promote proliferation and collateralization of capillary lymphatics in the superficial dermis. These vessels effectively bypass the zone of obstruction and prevent development of overt lymphedema (Fig. 27.14).³⁸ However, in the fraction of patients (30–50%) who go on to develop clinically measurable lymphedema, sustained interstitial fluid stasis and ongoing chronic inflammation lead to extracellular matrix collagen deposition with resultant obliteration of capillary lymphatics and smooth muscle cell proliferation around collecting lymphatics.³⁹ Thus, we and others hypothesize that development of clinically evident lymphedema is dependent on the failure of both superficial and deep lymphatic systems (i.e. capillary and collecting lymphatics, respectively) (Fig. 27.15). Patients have overt accumulation of interstitial fluid in the subcutaneous tissues (stage II) and changes in limb volume or circumference become possible by conventional measures. Interstitial fluid accumulates primarily (60–70% of the total excess volume) in the subcutaneous tissues between adipose tissues and around small veins.⁴⁰ To a lesser degree, fluid also accumulates above/below the muscular fascia and in the dermis. Collecting lymphatic vessels at this stage continue to actively contract; however, these contractions are ineffective and fail to propel lymphatic fluid forward.

Progression of lymphedema occurs as a result of accumulation of adipose tissues, hyperkeratosis, fibrosis, and progressive destruction/dysfunction of the remaining lymphatic

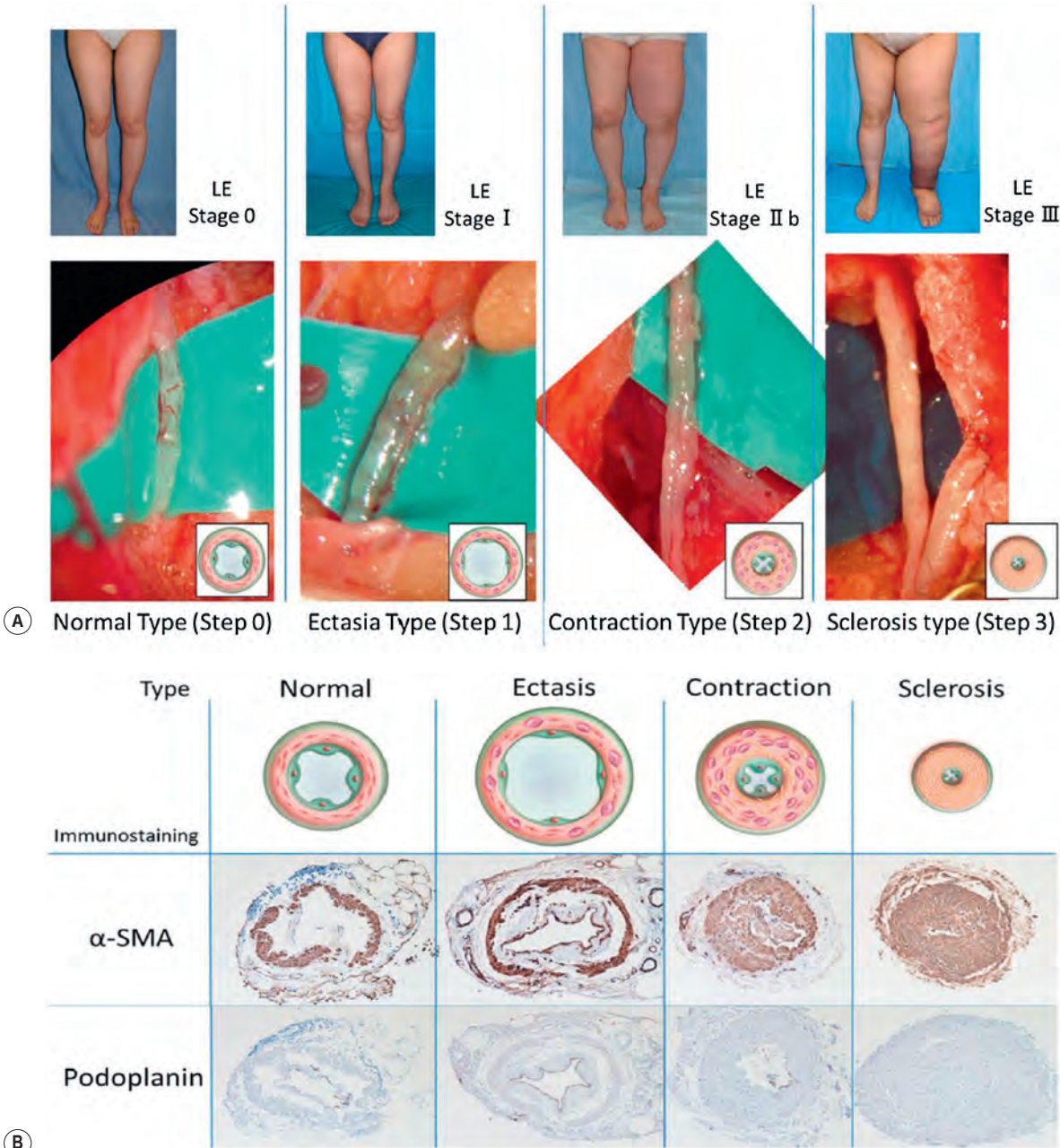


Fig. 27.11 (A) NECST classification of lymphedema. Upper panel shows representative figures of patients with various stages of lymphedema. Lower panel shows collecting lymphatic vessels corresponding to these stages. Note progressive sclerosis of the collecting lymphatics. (B) Histological changes in collecting lymphatics in the NECST classification scheme. Note increasing deposition of smooth muscle actin around the lymphatic vessels with increasing stage. (Adapted from Mihara M, Hara H, Hayashi Y, et al. Pathological steps of cancer-related lymphedema: histological changes in the collecting lymphatic vessels after lymphadenectomy. PLoS One. 2012;7:e41126.)

vessels (i.e. late stage II to III disease) (Fig. 27.16). The proportion of fluid versus fat accumulation is variable in different individuals and can have widely different patterns of deposition in the limb although some regions tend to swell more than others (i.e. medial elbow area). In addition, progressive fibrofatty deposition makes lymphedema therapy more resistant to compressive therapies. This problem is compounded by the presence of absent pulsations or completely sclerosed collecting lymphatics with loss of luminal diameter⁴¹ and absence of spontaneous lymph flow.

Regulation of fibrosis

Based on the evidence cited above, it is clear that extracellular matrix fibrosis and progressive sclerosis of collecting lymphatics play a key role in the pathology of lymphedema. This idea also provides a rationale for the increased risk of lymphedema in patients who have undergone radiation therapy and is supported by experimental studies demonstrating that fibrosis independently decreases lymphatic vessel regeneration and lymphatic function.^{42,43} Lymphedema may therefore

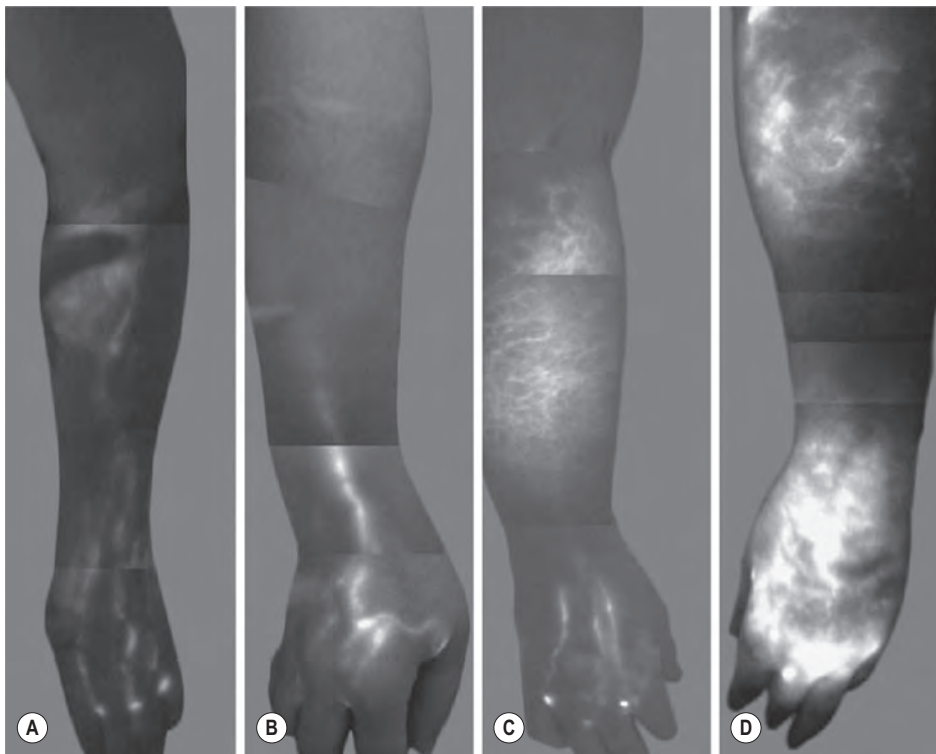


Fig. 27.12 M.D. Anderson ICG lymphedema classification system. (A) Stage 1: many patent lymphatic vessels and minimal dermal backflow. (B) Stage 2: moderate number of patent lymphatic vessels and presence of segmental dermal backflow. (C) Stage 3: few patent lymphatics and extensive dermal backflow in the entire arm. (D) Stage 4: no patent lymphatics and severe dermal backflow. (Adapted from Chang DW, Suami H, Skoracki R. A prospective analysis of a 100 consecutive lymphovenous bypass cases for the treatment of extremity lymphedema. *Plast Reconstr Surg.* 2013;132:1305–1314.)

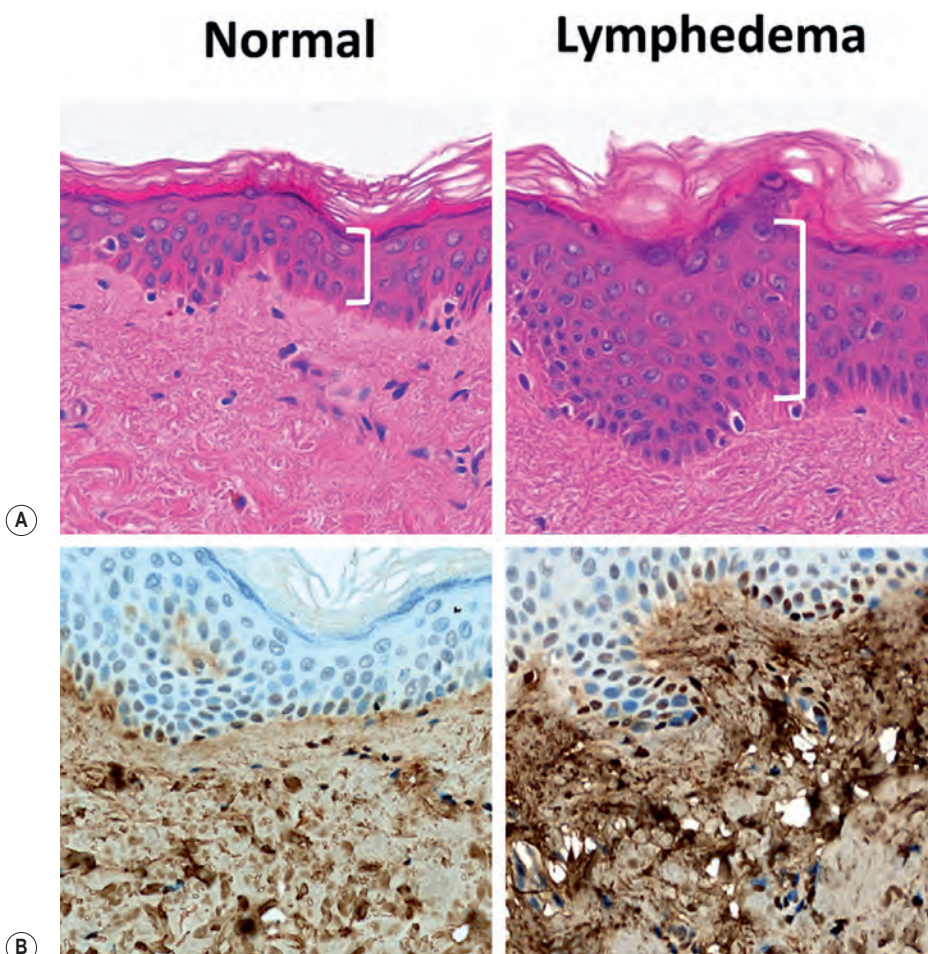


Fig. 27.13 Histology of lymphedema. (A) H&E stain of forearm skin demonstrating characteristic hyperkeratosis of lymphedematous skin (white brackets). (B) Forearm skin sections stained for type I collagen (brown stain). Note dermal accumulation of type I collagen.

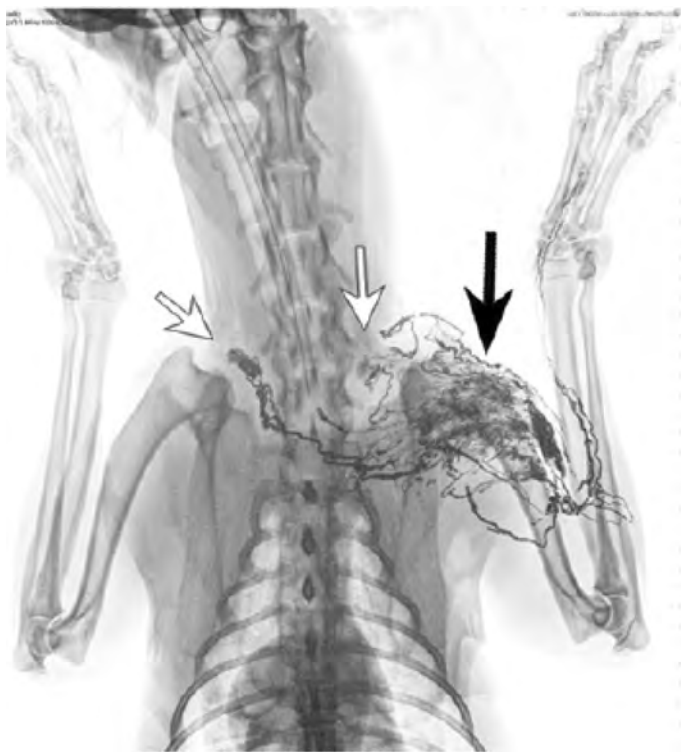


Fig. 27.14 Photograph of lymphangiography performed in a canine model of right axillary lymph node dissection demonstrating hyperplastic superficial lymphatic vessels (black arrow) bypassing the right axilla to lymph nodes in the supraclavicular area bilaterally (white arrows). (Adapted from Suami H, Yamashita S, Soto-Miranda MA, Chang DW. Lymphatic territories (lymphosomes) in a canine: an animal model for investigation of postoperative lymphatic alterations. *PLoS One*. 2013;8:e69222.)

simply be a fibrotic disorder with loss of functional parenchyma (i.e. capillary and collecting lymphatics) due to progressive fibrosis.

Using a variety of mouse models as well as clinical biopsy specimens, our lab has shown that lymphedema results in progressive fibrosis and that inhibition of this fibrotic response markedly increases lymphatic regeneration and function. In addition, we have shown that fibrosis in lymphedema is mediated by a proliferation of CD4+ cells that differentiate into a particular type of T-helper cell (Th2 cell) which in turn produces vast amounts of profibrotic cytokines such as interleukin 4, interleukin 13, and transforming growth factor beta-1.⁴⁴⁻⁴⁶ Treatment of lymphedema patients with lympho-venous bypass procedures is not only associated with symptomatic improvement, but also decreased accumulation of

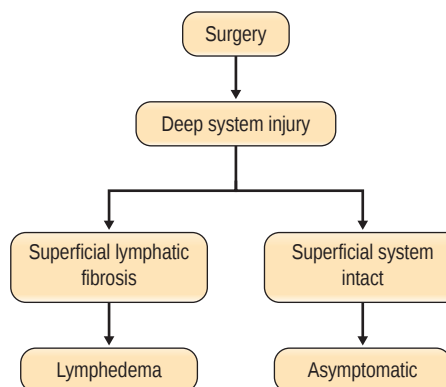


Fig. 27.15 Hypothetical model for development of lymphedema after failure of both deep and superficial lymphatic function.

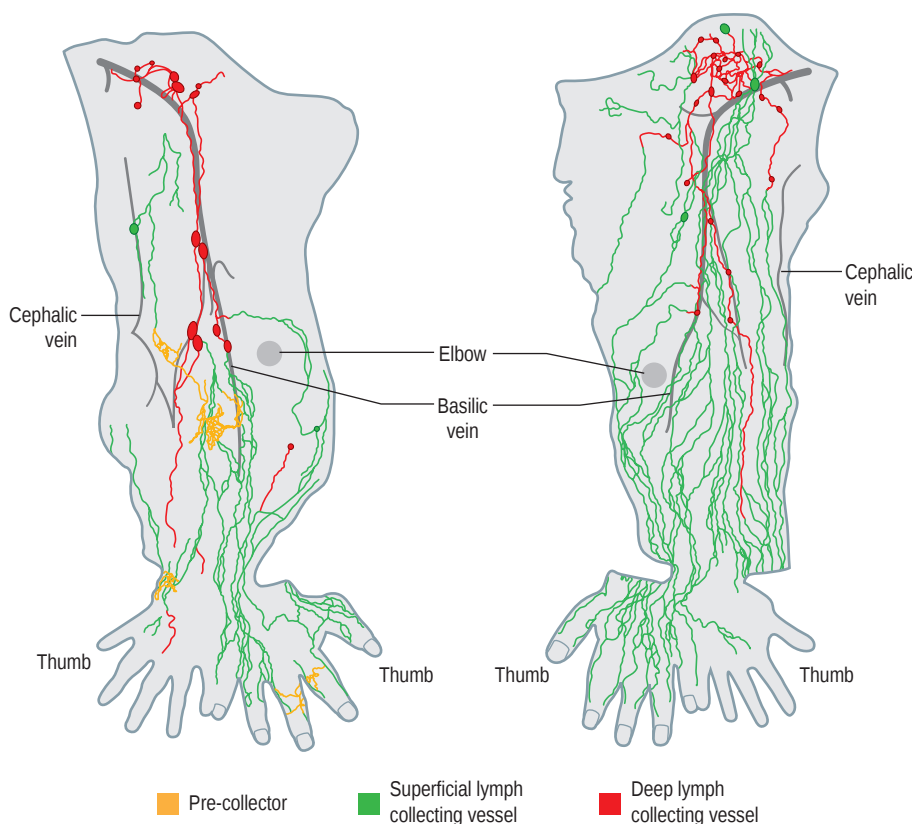


Fig. 27.16 Cadaver dissection and lymphangiography in a patient with a history of unilateral axillary lymph node dissection. Note loss of capillary (superficial) lymphatics stained green in the upper limb after lymph node dissection. (Adapted from Suami H, Pan WR, Taylor GI. Changes in the lymph structure of the upper limb after axillary dissection: radiographic and anatomical study in a human cadaver. *Plast Reconstr Surg*. 2007;120:982-991.)

CD4+ cells and fibrotic tissue. This observation, together with our previous animal studies demonstrating that depletion of CD4+ cells or inhibition of Th2 profibrotic cytokines markedly decreases the symptoms of lymphedema, may serve as a useful clinical intervention. This approach is currently under investigation in a clinical trial using monoclonal antibodies. Thus, pharmacological interventions may be a viable means of treating lymphedema or may serve as an important adjunct to surgery.

Regulation of adipose deposition

The end stage of lymphedema is progressive fibroadipose deposition. Thus, the initial pathology of lymphedema is accumulation of interstitial fluid; however, over time this fluid promotes adipose deposition rendering compressive treatments for lymphedema obsolete. It is clear, therefore, that lymphatic (interstitial) fluid accumulation and adipose deposition are closely related.^{47,48} This idea is supported by previous studies demonstrating that interstitial fluid potentially increases adipocyte proliferation and differentiation *in vitro*.⁴⁹ In addition, our lab has previously shown that lymphedema results in proliferation and hypertrophy of local adipocytes and that even mild lymphatic injury promotes expression of adipocyte differentiation markers.^{49–51}

The relationship between adipocytes and lymphatic endothelial cells appears to be bidirectional in nature. This hypothesis is based on recent reports demonstrating that obesity markedly impairs lymphatic function both clinically and in animal models. In addition, recent studies have shown that super obese individuals (i.e. BMI >59) spontaneously develop lower extremity lymphedema and that this effect is permanent with little improvement after gastric bypass and weight loss. More recently our lab has shown that lymphatic function is directly proportional to body weight in mice and that a threshold exists beyond which abnormalities in the lymphatic system are easily measureable. These findings provide a rationale for the fact that obesity is a major risk factor for lymphedema.

Risk factors for lymphedema

A variety of genetic and environmental factors have been shown to increase the risk of developing lymphedema including obesity, radiation, infection, and genetic factors.^{3,52–58}

Obesity

Obesity is among the first recognized risk factors for lymphedema⁵⁹ and has since been shown to increase the risk of disease in patients treated for a variety of solid tumors. Prospective studies have shown that patients with a body mass index (BMI) of >30 have at least a threefold increased risk of developing lymphedema as compared with patients with a similar stage breast cancer but a BMI of <25.⁶⁰ Other studies have shown that this relationship is almost linear with higher baseline weight being correlated with development of lymphedema after axillary lymph node dissection for breast cancer.³ Greene and colleagues have shown that massively obese patients (BMI >59) in some cases spontaneously develop lower extremity lymphedema.⁶¹ Even postoperative weight gain in previously lean patients increased the risk

of lymphedema development. Further, randomized clinical trials have shown that diet-induced weight loss over a 12-week period resulted in a significant reduction in arm volumes as compared to controls who did not lose weight.⁶² Finally, exercise studies have shown monitored exercise programs in lymphedema patients not only led to weight loss but also markedly decreased lymphedema symptoms as compared to a sedentary control group. Thus, although the cellular mechanisms regulating the interaction between obesity and lymphatic function remains unknown, it is clear that a relationship does exist and that patients who are scheduled for lymphadenectomy or lymphatic surgery should be counseled to first lose weight prior to proceeding with invasive interventions.

Radiation

Radiation therapy in combination with surgery is also a well-known risk factor for development of lymphedema, increasing the risk of disease development by as much as fivefold.^{63–66} Interestingly, lymphedema is significantly more prevalent in obese patients treated with surgery and radiation, suggesting that risk factors for lymphedema can act in an additive manner.⁶⁷ Although some studies have failed to show a relationship between radiation and development of lymphedema after breast cancer treatments, some of these results may be confounded by the fact that radiation in some studies included only the chest wall and not the regional lymph node basins (e.g. supraclavicular or axilla). In addition, it appears that the negative effects of radiation on lymphedema development are largely additive to those of surgery since the development of the disease following radiation alone is unusual, occurring in less than 7% of patients.⁶⁶

Infection

Postoperative infections and cellulitis have long been thought to be a risk factor for development of lymphedema, however the mechanisms that regulate this potential interaction remain unknown. In addition, it is unknown if development of an infection is a symptom of subclinical lymphedema that eventually blossoms into full scale disease or if infection damages remaining lymphatics thus resulting in disease development. Nevertheless, previous gynecological reports have shown that early infections following vulvar cancer surgery significantly increase the incidence of lower extremity lymphedema development.⁶⁸ These findings have led some investigators to suggest that avoiding cellulitis is a major method to avoid lymphatic injury and disease progression, particularly in patients with a previous history of lymphedema.⁶⁹

Genetics

Genetics have long been shown to cause primary lymphedema and lymphatic abnormalities. However, more recent studies have identified genetic factors that also predispose patients to developing *secondary lymphedema*. For example, Finegold *et al.* found that women with mutations in the gene encoding for connexin 47 or hepatocyte growth factor have a significantly increased risk of developing lymphedema after mastectomy and axillary lymph node dissection as compared with normal controls.^{70,71} Another studied 157 single-nucleotide polymorphisms (SNPs) in 17 candidate genes and demonstrated that at least four genes and three haplotypes may contribute to

development of secondary lymphedema.⁷² By providing evidence for genetic mutations as an important risk factor in secondary lymphedema, these new discoveries challenge the traditional perspective of secondary lymphedema being solely due to mechanical trauma.⁷²

Summary

Lymphedema is a debilitating and common disease that occurs most commonly as a complication of cancer care.

Recent studies have shown that the pathophysiology of lymphedema is related to lymphatic vessel dilation, valvular incompetence, chronic inflammation and fibrosis. Treatment strategies aiming to decrease these changes (e.g. manual lymphatic massage or compressive pumps) decrease the rate of progression of disease and are helpful adjuncts to therapy. In addition, a better understanding of the pathophysiology of lymphedema may enable development of targeted preventative or therapeutic strategies.



Access the complete reference list online at <http://www.expertconsult.com>

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Benign and malignant nonmelanocytic tumors of the skin and soft tissue

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SYNOPSIS

- All typical skin and skin-associated soft-tissue tumors, apart from malignant melanocytic tumors (malignant melanoma), are described from the point of view of a plastic surgeon.
- Biopsies should only be performed for a clear purpose, such as for the differential diagnosis of benign tumors or to analyze the stage and grade of malignant tumors, which would allow the area to be resected to be determined.
- One current and useful model is the reconstructive matrix, which helps plastic surgeons to determine the best reconstructive solutions for their patients in the context of particular medical and socioeconomic environments by considering aspects of surgical complexity, technological sophistication, and patient surgical risk.

Introduction

The skin consists of the epidermis, which is derived during ontogeny from the superficial ectoderm, and the dermis, which is derived from the mesenchyme. Starting in the first 3–4 weeks of human ontogeny, cells derived from the neural crest migrate into the epidermis (Fig. 28.1) where they become melanocytes and Schwann cells; the latter associate with peripheral nerves in the skin. Later, the cutaneous appendages develop. These include hair, which originates from epidermal cells, and hair papillae, which are filled with mesenchyme; vessels and peripheral nerve endings also develop in the papillae. Other cutaneous appendages are the sebaceous glands, which are derived from the epithelial wall of the hair papillae, and the eccrine and apocrine sweat glands, which are also epidermal in origin. There are also soft tissues that are associated with skin, namely fat, muscles, and blood vessels (all of which have a mesenchymal lineage) and nerves (derived from neural crest cells). Thus, skin and skin-associated soft-tissue tumors can be classified simply into those that are of epithelial, cutaneous appendage, neural crest, and mesenchymal origin (Fig. 28.2).

In this chapter, all typical skin and skin-associated soft-tissue tumors apart from malignant melanocytic tumors (malignant melanoma) are described from the point of view of the plastic surgeon.

Diagnosis

Inspection and palpation

The diagnosis of skin tumors starts with inspection and palpation. The following information should be recorded: the number of lesions (solitary or multiple), the shape of the lesion (e.g., round, oval, polygonal, geographic, linear, annular), its size, its elevation status (e.g., narrow-pediced, wide-pediced, dome-like, hemispherical, flat elevated, umbilicated), its surface status (e.g., smooth, rough, papillary, granular, transudatory, xerophily, ulcerative, erosive, atrophic, lustrous, necrotic), its color (e.g., normal, yellow, pale yellow, erythematous, blackish brown, black, blue, depigmented, pigmented, hyperemic, livid), its hardness (e.g., soft, elastic soft, elastic hard, hard, bone-like hard, fluctuating), its alignment (e.g., localized, disseminated, centrifugal, systematized, singular, symmetric, asymmetric, bilateral), its site, whether there are any subjective symptoms (e.g., pain, itch, contracture sensation, numbness, burning sensation, cold sensation), and the time course of the appearance of the lesion (e.g., acute, subacute, chronic, temporary, recurrent). Color plays a particularly important role in the diagnosis of skin lesions (Box 28.1). The possibility of malignant tumors should be suspected at all times. If the shape, size, elevation status, or color of a lesion changes rapidly, a biopsy should be considered.

Dermoscopy

Dermoscopy is a specialized technique that employs a binocular microscope to observe the skin surface. It is useful for diagnosing pigmented lesions and is necessary for differentially diagnosing malignant melanoma and nevus. It is also

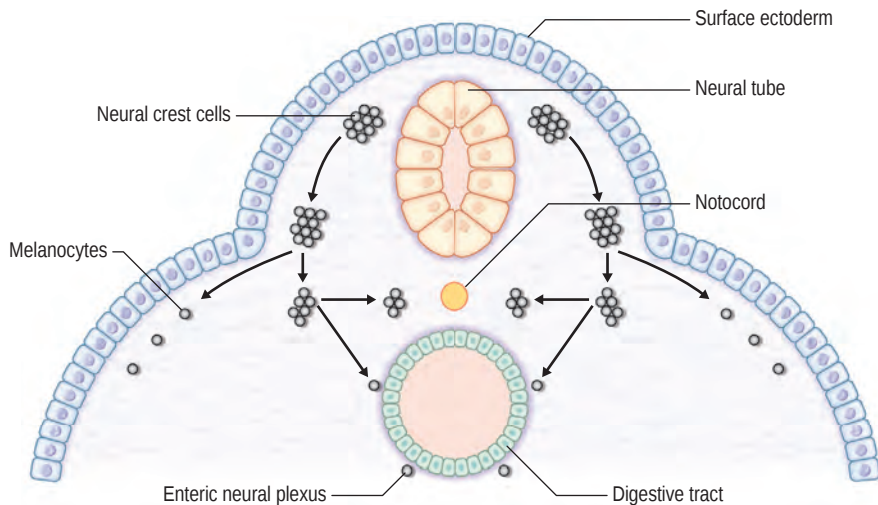


Fig. 28.1 The human embryo at 3–4 weeks.

required for the diagnosis of seborrheic keratosis, basal cell carcinoma (BCC) and vascular lesions. Marghoob *et al.*¹ has recommended the use of a revised two-step diagnostic algorithm, in which the first step is to differentiate melanocytic from nonmelanocytic pigmented lesions by using specific dermoscopic criteria. The second step is to differentiate between the various nonmelanocytic lesions by using other specific dermoscopic criteria (Fig. 28.3). The dermoscopic criteria that are used to diagnose melanocytic lesions, seborrheic keratosis, BCC, and vascular lesions are shown in Box 28.2.

Ultrasound and Doppler imaging

To observe skin lesions, high-frequency ultrasound around 20–50 MHz is needed.² However, if the lesion shows extension

perpendicular to the skin surface that exceeds a depth of 20 mm, the standard ultrasound (3–10 MHz) should be used. In such cases, computed tomography (CT) and magnetic resonance imaging (MRI) can provide additional information. Ultrasound can be used to determine tumor thickness, its relationship with adjacent structures, and the presence of lymph node metastasis. A variety of ultrasound devices are suitable for this purpose, including mechanical or electron scanning, one-dimensional A-mode, two-dimensional B-mode, and three-dimensional C-mode devices.

Doppler imaging using color Doppler imaging (CDI) or power Doppler imaging is useful for the differential diagnosis of benign and malignant skin tumors, assessing inflammatory reactions, and detecting lymph node metastases. This is because 90% of malignant skin tumors exhibit a high blood flow rate of 3–20 cm/s that is not observed in more than 95%

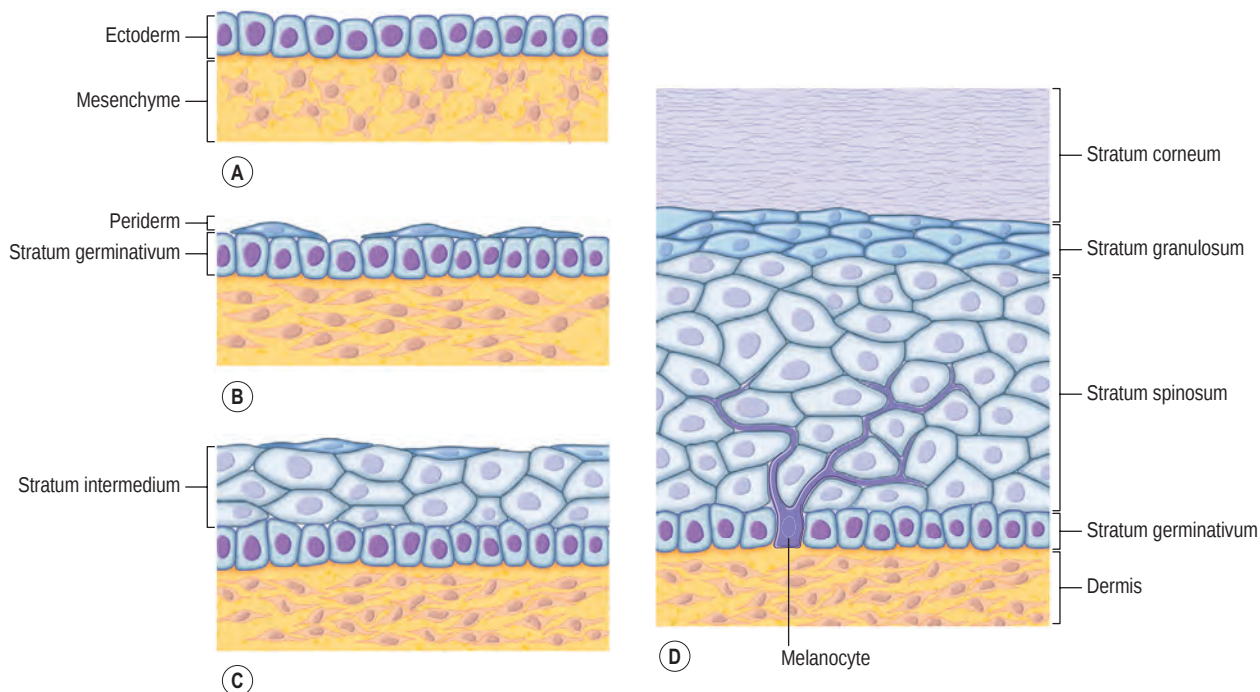


Fig. 28.2 Development of the skin. (A) The fifth week of fetal life. (B) The seventh week of fetal life. (C) The fourth month of fetal life. (D) At birth.

BOX 28.1 Typical skin tumor colors**Normal color**

Epidermal origin (e.g., epidermoid cyst)
 Mesenchymal origin (e.g., lipoma, soft fibroma, leiomyoma)
 Neural crest origin (e.g., schwannoma)

Yellow–pale yellow

Appendage origin (e.g., sebaceous nevus, xanthoma, milia)

Erythematous

Epidermal origin (e.g., inflammatory atheroma, squamous cell carcinoma)
 Mesenchymal origin (e.g., keloid and hypertrophic scars, vascular malformations, hemangioma, dermatofibrosarcoma protuberans, angiosarcoma)

Blackish brown–black

Epidermal origin (e.g., basal cell carcinoma)
 Neural crest origin (e.g., pigmented nevus, melanoma)

Blue

Epidermal origin (e.g., epidermoid cyst)
 Neural crest origin (e.g., nevus of Ota, Mongolian spot, blue nevus)

BOX 28.2 Dermoscopic criteria used to diagnose melanocytic lesions, seborrheic keratosis, basal cell carcinoma, and vascular lesions**Criteria for melanocytic lesions**

Pigment network
 Negative network
 Aggregated globules
 Streaks
 Homogeneous blue pigmentation
 Pseudonetwork
 Parallel pattern

Criteria for seborrheic keratosis

Multiple milia-like cysts
 Comedo-like openings
 Light-brown fingerprint-like structures
 Fissures/ridges

Criteria for basal cell carcinoma

Pigment network is absent and one of:
 Arborizing vessels
 Leaf-like areas
 Large blue-gray ovoid nests
 Multiple blue-gray globules
 Spoke wheel areas
 Ulceration

Criteria for vascular lesions

Red–blue lacunas
 Red–bluish to red–black homogeneous areas

(Reproduced from the Consensus Net meeting on Dermoscopy, 2000. Available at: <http://www.dermoscopy.org/consensus/>.)

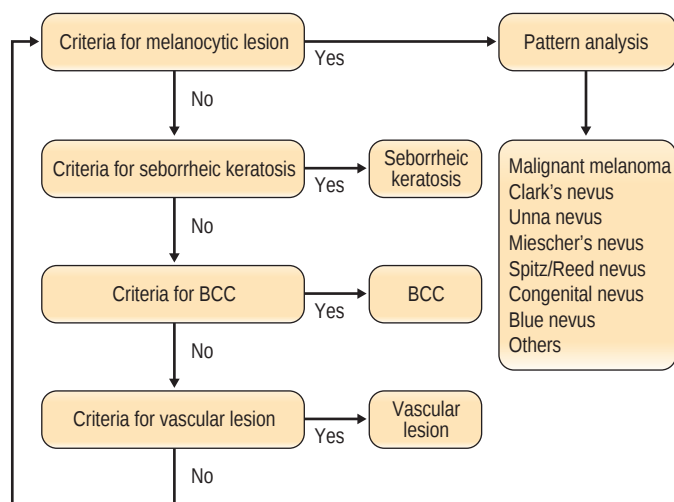


Fig. 28.3 Two-step diagnosis using dermoscopy. BCC, basal cell carcinoma. (Modified from Consensus Net meeting on Dermoscopy. Available at <http://www.dermoscopy.org/consensus/>.)

of benign skin tumors. The resolution of power Doppler imaging is higher than that of CDI. M-mode and duplex (a combination of B- and M-mode) scanning are useful for observing hemangiomas or vascular malformations.

X-ray, CT, MRI, angiography, scintigraphy, and positron emission tomography (PET)

X-ray analysis is useful for detecting calcifying lesions such as pilomatricoma and malignant tumors that have necrosis-induced calcifications. Moreover, bone deformation associated

with malignant or nonmalignant tumor invasion into bones can be observed by using X-rays.

CT detects metastatic lesions in the bone, lymph nodes, and lungs better than MRI. Helical CT or multidetector low CT can generate three-dimensional and high-resolution images. Contrast-enhanced CT and CT angiography are useful for detecting malignant tumors, vascular regions, and adjacent vascular structures.

MRI detects soft tissues better than CT. In general, malignant tumors present with low-iso signal intensity on T2-weighted images (T2WI) and low signal intensity on T1-weighted images (T1WI), while benign tumors exhibit high signal intensity on T2WI and low signal intensity on T1WI. Magnetic resonance angiography is superior to MRI in determining the nidus and exact nature of the collateral structures in hemangiomas and vascular malformations.

Angiography is an invasive imaging method that was frequently used in the past to investigate vascular lesions. While it detects hemangiomas and vascular malformations readily, its use with pediatric patients requires general anesthesia.

Scintigraphy can be used for metastatic lesion screening. ^{67}Ga and $^{201}\text{TlCl}$ are used in tumor- or inflammation-seeking scintigraphy, while $^{99}\text{Tc-MDP}$ and $^{99\text{m}}\text{Tc-HMDP}$ are used in bone scintigraphy. Scintigraphy suffers from low resolution, and this makes it difficult to detect lesions that are less than 2 mm in diameter by this method.

PET is also useful for detecting the metastatic lesions of malignant skin tumors.³ 2-deoxy-2-[^{18}F] fluoro-D-glucose (FDG) PET (FDG-PET) has been used for the diagnosis and staging of cancers and for monitoring treatment, particularly with regard to Hodgkin's lymphoma, non-Hodgkin's lymphoma, and lung cancer. PET can also sometimes detect many other types of solid tumors that occasionally show up as very highly labeled lesions. FDG-PET is particularly useful for searching for tumor metastasis, or for recurrence after the removal of a primary tumor that was known to be highly active. However, since PET can also detect inflammatory lesions, it will be necessary to exclude the possibility that a PET-detected apparent tumor is not an inflammatory, erosive, or ulcerated area.

Pathologic diagnosis

A definitive diagnosis requires a pathologic diagnosis. However, biopsies should only be performed for a clear purpose, such as for the differential diagnosis of benign tumors or to analyze the stage and grade of malignant tumors, which would allow the area to be resected to be determined. Moreover, biopsies should only take place after careful inspection, palpation, and imaging analyses. Depending on the purpose of a biopsy and the lesion characteristics, the surgeon can choose from a range of different biopsy techniques, including punch, incisional, excisional, and mapping biopsies. In the case of incisional biopsies, normal skin should be excised together with early-stage lesions and the characteristic areas of lesions (e.g., inflammatory, erosive, or ulcerated areas).

In the case of a possible malignant tumor, an excisional biopsy is recommended to prevent malignant cell dissemination into blood. However, surgeon judgment is needed to determine the amount of normal skin that should be removed. In general, the normal skin margin of an excisional biopsy should be as minimal as possible, especially if the tumor is suspected to be benign. However, if the margins of an excisional biopsy of a malignant tumor are wide enough, such biopsies could actually serve the same purpose as radical resections. Such extensive excisional biopsies could also reduce the number of operations that are needed to treat a tumor. Thus, if a low-grade malignant tumor (e.g., BCC) is suspected, an excisional biopsy that includes several millimeters of normal skin margin may be considered. For high-grade malignant tumors, excisional biopsies will often lead to a pathologic diagnosis that indicates the need for additional wide resection, radiation therapy, and/or chemotherapy.

Sentinel node biopsy is increasingly being used to detect lymph node metastasis, as it shows whether the cancer has spread to the very first lymph node.⁴ If the sentinel lymph node does not contain cancer, it is highly likely that the cancer has not spread to any other area of the body. However, this technique is only of therapeutic value for patients with positive nodes: for patients who have negative nodes, the possibility

that the lymph node has undetectable cancerous cells should be considered. In addition, there is no compelling evidence that the survival of patients who have a full lymph node dissection as a result of a positive sentinel lymph node biopsy is better than that of those patients who do not have a full dissection until later in the disease, when the lymph nodes can be felt by a physician. Thus, such patients may be subjected unnecessarily to full dissection, which is associated with lymphedema.

The TNM clinical classification system and the pTNM pathologic classification system

The TNM clinical classification^{5,6} applies only to malignant tumors (Figs. 28.4 & 28.5). T indicates the size of the tumor and whether it has invaded nearby tissue, N indicates whether regional lymph nodes are involved, and M indicates the presence of distant metastasis. The TNM classification system is based on clinical evidence acquired before definitive treatment. Once intraoperative and surgical pathologic data become available, the pathologic TMN (pTNM) classification system can be used. The pT, pN, and pM categories correspond to the T, N, and M categories.

Regional lymph nodes are those that drain the site of the primary tumor (Fig. 28.6). The pN assessment of the regional lymph nodes requires that a sufficient number of lymph nodes are removed for histologic examination (usually six or more). If the examined lymph nodes are negative but fewer than six lymph nodes were resected, the pN classification is designated pN0.

Box 28.3 shows examples of the TNM classification system, namely the systems used for eyelid, vulva, penis, and soft-tissue sarcomas.

Clinical staging

The TNM system^{5,6} is used to show the anatomical extent of malignant tumors. For purposes of tabulation and analysis, it is useful to condense these categories into stages (Table 28.1). To be consistent with the TNM system, carcinoma *in situ* is categorized as stage 0. In general, tumors that are localized to the organ of origin are categorized as stages I and II, while those that exhibit extensive local spread, particularly to the regional lymph nodes, are classified as stage III. The tumors that have distant metastasis are classified as stage IV. For pathological stage groups, if sufficient tissue has been removed for pathological examination to evaluate the highest T and N categories, M1 may be either clinical (cM1) or pathological (pM1). However, if only a distant metastasis has had microscopic confirmation, the classification is pathological (pM1) and the stage is pathological.

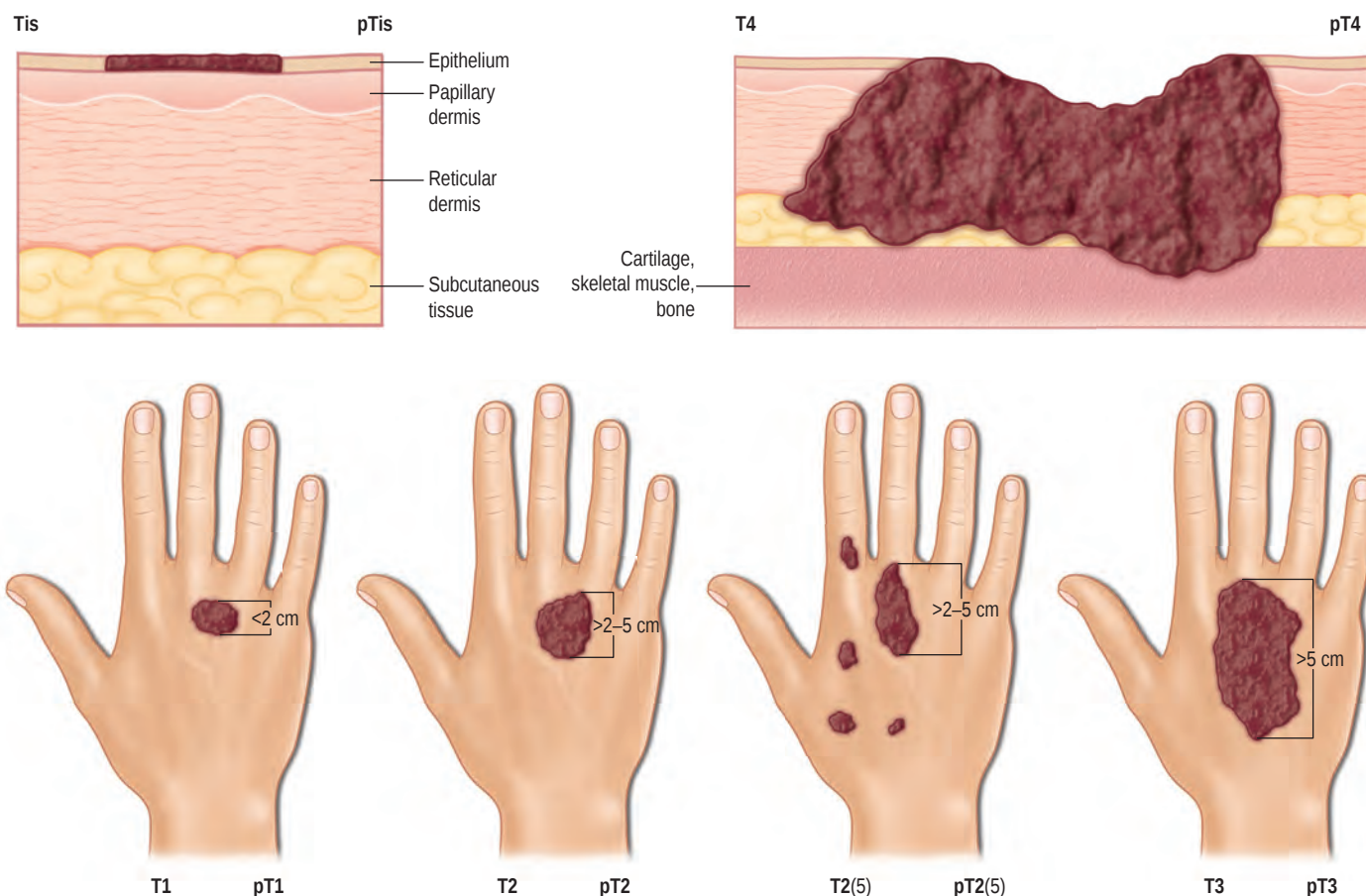
Treatment

Wide excision

With regard to wide resection of malignant tumors of skin, the horizontal and vertical margins vary depending on the type of tumor.⁷⁻⁹ Retrospective histopathologic studies have supported reductions in the horizontal margin in recent

T – Primary tumor*

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	The greatest dimension of the tumor is 2 cm or less
T2	The greatest dimension of the tumor is more than 2 cm but less than 5 cm
T3	The greatest dimension of the tumor is more than 5 cm
T4	The tumor invades deep extradermal structures such as cartilage, skeletal muscle, or bone



* In the case of multiple simultaneous tumors, the tumor with the highest T category is used for the classification and the number of separate tumors is indicated in parentheses (e.g., T2 (5))

Fig. 28.4 The T factor of the TNM classification system, as described by the Union for International Cancer Control (UICC). (Used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. Original source: Wittekind CF, Greene FL, Hutter RVP, et al. TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours, 5th edition. Berlin: Springer; 2004.)

years. The horizontal margins that are recommended for particular tumor types are listed in [Box 28.4](#). In the case of malignant soft-tissue tumors, the type of excision can vary with regard to the extent of the margins around the tumor: curative wide, wide, and marginal excisions indicate margins that are at least 5 cm outside the tumor-reactive layer, 1–2 cm outside the tumor-reactive layer, and within the tumor-reactive layer, respectively. It is now considered that wide excision is the appropriate margin for soft-tissue sarcoma. Moreover, Mohs micrographic surgery, where tumors undergo histologic analysis during surgery in such a way that almost all of the surgical margins can be examined for tumor extensions, can help to obtain complete margin control during the removal of a skin cancer and soft-tissue sarcoma.¹⁰

Lymph node dissection

Axillary lymph node dissection

Since sentinel lymph node biopsy is now a widely practiced technique, there are fewer occasions where preventive axillary lymph node dissection is necessary. Metastatic squamous cell carcinoma (SCC) is an example of a malignant nonmelanocytic skin tumor that warrants axillary lymph node dissection. Axillary lymph nodes can be classified into levels I, II, and III, which relate to the lateral and internal edges of the pectoralis minor muscle. Level I is the bottom level and lies below the lower edge of the pectoralis minor muscle. Level II lies underneath the pectoralis minor muscle, while level III is above the pectoralis minor muscle. Structures that should be preserved

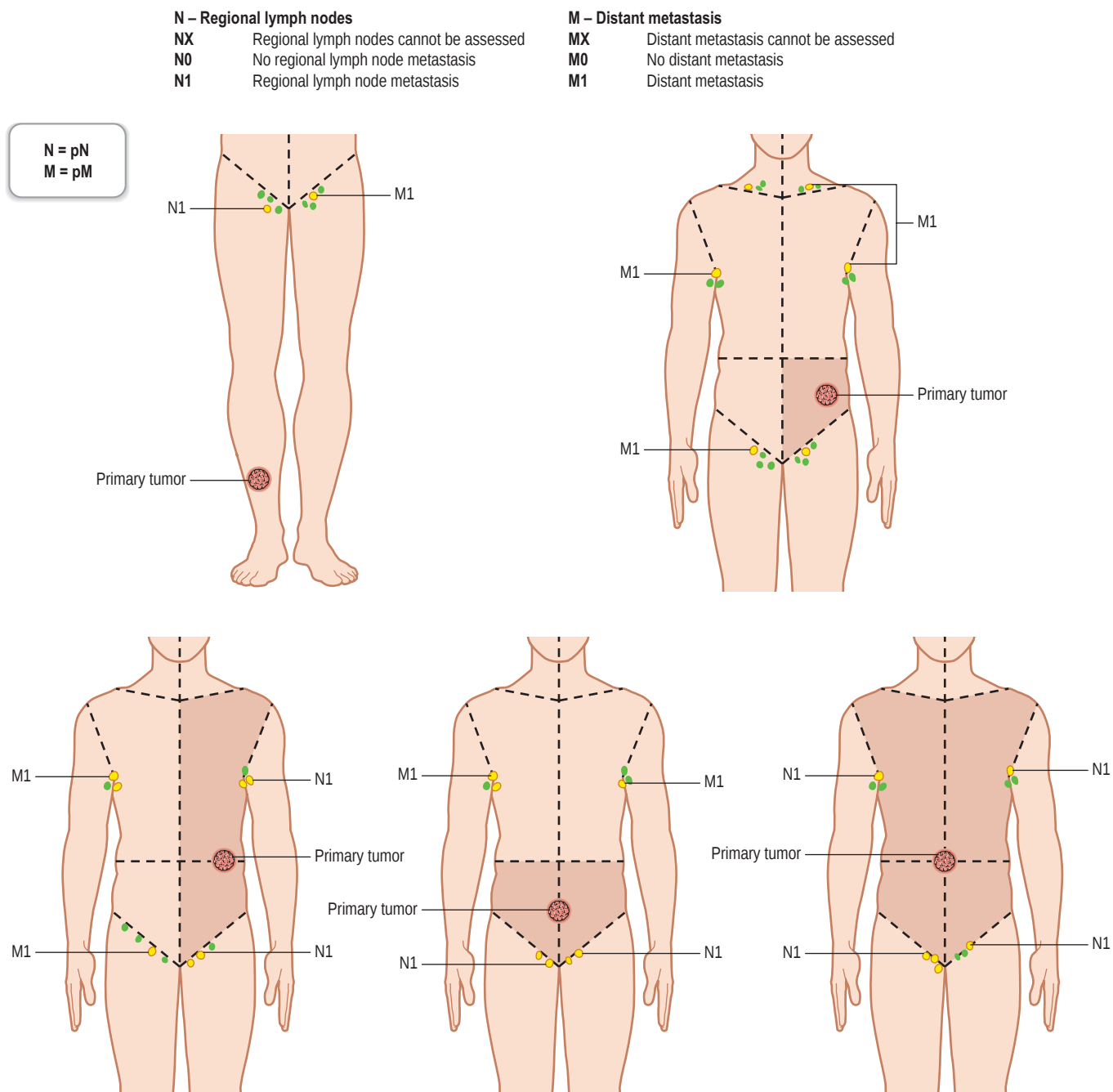


Fig. 28.5 The N and M factors of the TNM classification system, as described by the Union for International Cancer Control (UICC). (Used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. Original source: Wittekind CF, Greene FL, Hutter RVP, et al. TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours, 5th edition. Berlin: Springer; 2004.)

during axillary lymph node dissection are the pectoral nerves, the long thoracic nerve, the intercostobrachial nerves, the axillary artery and veins, the thoracoacromial artery and veins, and the subscapular artery and veins.

Inguinal lymph node dissection

Widespread use of sentinel lymph node dissection has also reduced the frequency of inguinal lymph node dissection. Representative indications for inguinal lymph node dissection

are metastatic SCC and extramammary Paget's disease (EMPD). Traditionally, the area of dissection is a triangle composed of the inguinal ligament, the internal edge of the sartorius muscle, and the internal edge of the long adductor muscle. In the wide resection of inguinal lymph nodes, the femoral vein is identified along with the saphenous vein. After clamping the saphenous vein, the adductor longus muscle is identified and should be cleaned of all fatty nodal tissue by retracting the saphenous vein *en bloc* with the lymph nodes until the adductor canal is reached.

Unilateral tumors

Head, neck	Ipsilateral preauricular, submandibular, cervical, and supraclavicular lymph nodes
Thorax	Ipsilateral axillary lymph nodes
Upper limb	Ipsilateral epitrochlear and axillary lymph nodes
Abdomen, loins, and buttocks	Ipsilateral inguinal lymph nodes
Lower limb	Ipsilateral popliteal and inguinal lymph nodes
Anal margin and perianal skin	Ipsilateral inguinal lymph nodes

Tumors in the boundary zones

Between

Right / left midline

Head and neck / thorax	Clavícula–acromion–upper shoulder blade edge
Thorax / upper limb	Shoulder–axilla–shoulder
Thorax / abdomen, loins, and buttocks	Front: middle between the navel and the costal arch. Back: lower border of the thoracic vertebrae (midtransverse axis)
Abdomen, loins, and buttocks / lower limb	Groin–trochanter–gluteal sulcus

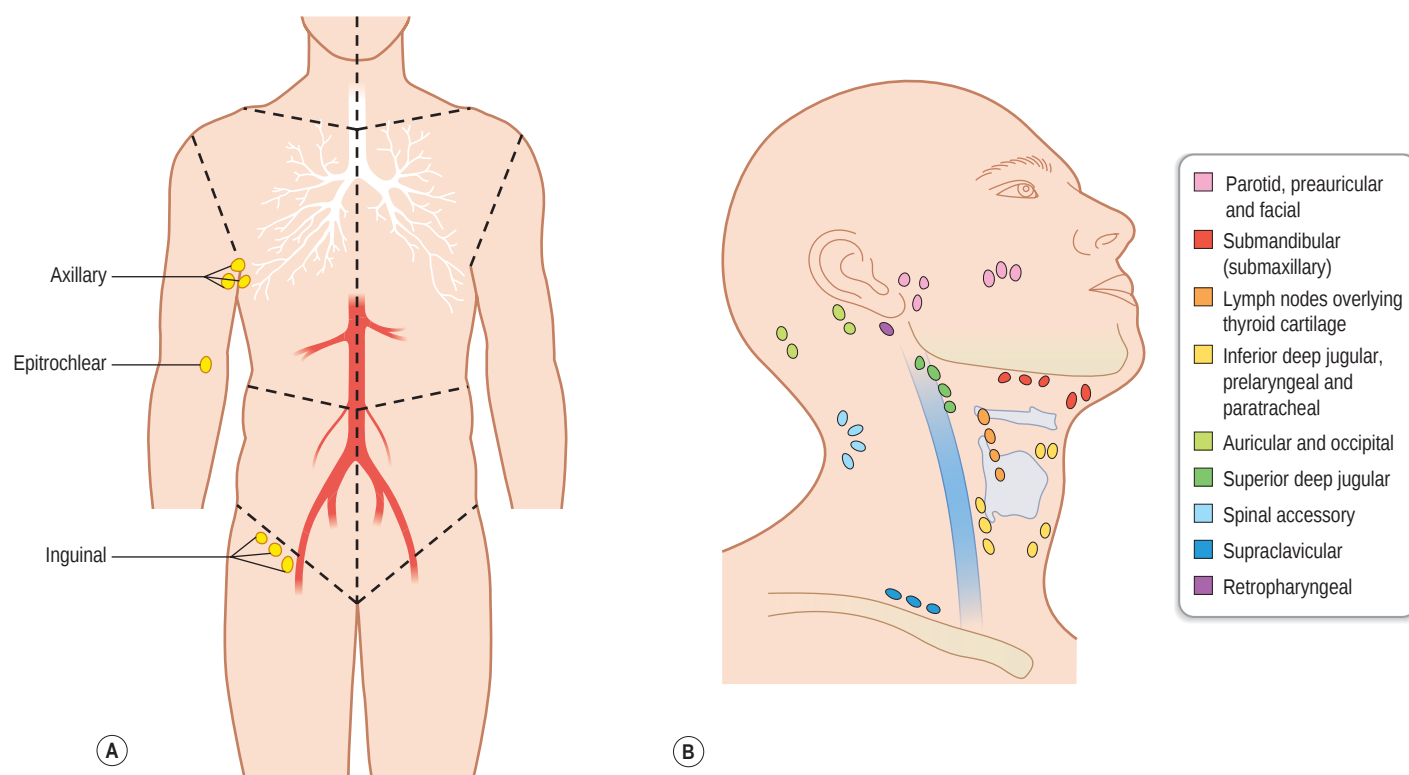


Fig. 28.6 The regional lymph nodes, as described by the Union for International Cancer Control (UICC). (Used with the permission of the Union for International Cancer Control (UICC), Geneva, Switzerland. Original source: Wittekind CF, Greene FL, Hutter RVP, et al. TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours, 5th edition. Berlin: Springer; 2004.)

Reconstructive surgery

Reconstruction via skin grafting is a basic surgical technique that is used to reconstruct the tissue defects that occur after tumor extirpation, which is also useful for early detection of local recurrence. The ideal approach after tumor extirpation is to suture the wound margins directly together. However, this can only be performed if the wound is not too big and the adjacent skin can be extended sufficiently. One concern with this approach is that malignant cells may be left in the deep margins of the wound. Recent developments in reconstructive techniques, including thin flap-based techniques and wound coverage materials, mean that plastic surgeons can now choose from a wide and rapidly evolving variety of primary and aesthetic secondary reconstruction methods. Given this constantly altering medical (and social) environment, it is difficult

to develop up-to-date reconstructive algorithms, and indeed, previous algorithms such as the reconstructive ladder, elevator, and triangle quickly lose favor. Consequently, the techniques that are chosen for primary and secondary reconstruction are largely determined on a case-by-case basis. However, one current and useful model is the reconstructive matrix,¹¹ which helps plastic surgeons to determine the best reconstructive solutions for their patients in the context of particular medical and socioeconomic environments by considering aspects of surgical complexity, technological sophistication, and patient surgical risk.

Radiation therapy

Malignant tumors vary in their sensitivity to radiation-induced damage, which directly affects the success of radiation therapy.

BOX 28.3 The TNM classification systems for eyelid, vulva, penis, and soft-tissue sarcomas (Union for International Cancer Control)**Carcinoma of the skin of the eyelid**

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*
- T1 The tumor is of any size and does not invade the tarsal plate; or the tumor is at the eyelid margin and its greatest dimension is 5.0 mm or less
- T2 The tumor invades the tarsal plate; or the tumor is at the eyelid margin and its greatest dimension is more than 5.0 mm but less than 10.0 mm
- T3 The tumor involves the full eyelid thickness; or the tumor is at the eyelid margin and its greatest dimension is more than 10.0 mm
- T4 The tumor invades adjacent structures, including the bulbar conjunctiva, sclera/globe, soft tissues of the orbit, perineural invasion, bone/periosteum of the orbit, nasal cavity/paranasal sinuses, and central nervous system
- N1 Regional lymph node metastasis

Carcinoma of the skin of the vulva

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*
- T1 The tumor is confined to the vulva, or the vulva and the perineum, and its greatest dimension is 2 cm or less
- T1a The tumor is confined to the vulva, or the vulva and perineum, its greatest dimension is 2 cm or less, and it exhibits stromal invasion that is no greater than 1.0 mm
- T1b The tumor is confined to the vulva, or the vulva and the perineum, its greatest dimension is 2 cm or less, and it exhibits stromal invasion that is greater than 1.0 mm
- T2 The tumor is confined to the vulva, or the vulva and the perineum, and its greatest dimension is more than 2 cm
- T3 The tumor invades the lower urethra, vagina, and/or anus
- T4 The tumor invades the bladder mucosa, rectal mucosa, and/or upper urethral mucosa, or is fixed to the pubic bone
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Unilateral regional lymph node metastasis
- N2 Bilateral regional lymph node metastasis

Carcinoma of the skin of the penis

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma *in situ*
- Ta Noninvasive verrucous carcinoma
- T1 The tumor invades the subepithelial connective tissue
- T2 The tumor invades the corpus spongiosum or cavernosum
- T3 The tumor invades the urethra or prostate
- T4 The tumor invades other adjacent structures
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single superficial inguinal lymph node
- N2 Metastasis in multiple or bilateral superficial inguinal lymph nodes
- N3 Metastasis in deep inguinal or pelvic lymph nodes, unilateral or bilateral

Soft-tissue sarcoma

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 The greatest dimension of the tumor is 5 cm or less
- T1a The tumor is superficial*
- T1b The tumor is deep*
- T2 The greatest dimension of the tumor is more than 5 cm
- T2a The tumor is superficial
- T2b The tumor is deep
- N1 Regional lymph node metastasis

*Superficial tumors are located exclusively above the superficial fascia and do not invade the fascia, while deep tumors are either exclusively beneath the superficial fascia, or are superficial to the fascia but invade into or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors. (Modified from Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours (UICC: Union for International Cancer Control)*, 7th edn. Chichester: Wiley-Blackwell; 2009; and Wittekind CF, Greene FL, Hutter RVP, et al (eds). *TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours*, 5th edn. Berlin: Springer; 2004.)

For example, malignant melanomas are less sensitive to radiation and are therefore rarely treated with radiation therapy. Malignant skin tumors that are relatively sensitive to radiation and are therefore commonly treated with radiation therapy include BCC,¹² SCC,¹³ and Merkel cell carcinoma of the skin.¹⁴ Acute skin reactions to radiation therapy occur during the first 7–10 days after treatment and are characterized initially by erythema that then progresses to pigmentation, epilation, and desquamation; this is particularly the case when higher doses are used. Subacute and late complications occur several weeks after radiation therapy and can progress for long periods of

time. These complications include scarring, permanent pigmentation, depigmentation, atrophy, telangiectasis, subcutaneous fibrosis, and necrosis.

Chemotherapy

Chemotherapy can be either adjuvant or primary, and all chemotherapies can be administered either systemically or topically. Adjuvant chemotherapy is mainly used for malignant melanoma, while primary chemotherapy is indicated for SCC,¹⁵ angiosarcoma,¹⁶ and EMPD.¹⁷ However, the radical

Table 28.1 Clinical staging (Union for International Cancer Control)

Carcinoma of the skin (general staging system)				Carcinoma of the skin of the vulva			
Stage 0	Tis	N0	M0	Stage 0	Tis	N0	M0
Stage I	T1	N0	M0	Stage I	T1	N0	M0
Stage II*	T2	N0	M0	Stage IA	T1a	N0	M0
Stage III	T3			Stage IB	T1b	N0	M0
	T1, 2, 3	N1	M0	Stage II	T2	N0	M0
Stage IV	T1, 2, 3	N2, 3	M0	Stage IIIA	T1, 2	N1a, 1b*	M0
	T4	AnyT	M0	Stage IIIB	T1, 2	N2a, 2b*	M0
	AnyT	AnyN	M1	Stage IIIC	T1, 2	N2c*	M0
The American Joint Committee on Cancer considers stage I tumors that have more than one high-risk feature to be stage II tumors.				Stage IVA	T1, 2	N3	M0
					T3	AnyT	M0
Merkel cell carcinoma of the skin				Stage IVB	AnyT	AnyN	M0
Stage 0	Tis	N0	M0	*N1a: 1–2 lymph node metastases, each with a greatest dimension less than 5 mm N1b: 1 lymph node metastasis whose greatest dimension is 5 mm or greater N2a: 3 or more lymph node metastases, each with a greatest dimension less than 5 mm N2b: 2 or more lymph node metastases whose greatest dimensions are 5 mm or greater N2c: Lymph node metastasis with extracapsular spread N3: Fixed or ulcerated regional lymph node metastasis			
Stage I	T1	N0	M0				
Stage IA	T1	pN0	M0				
Stage IB	T1	cN0	M0				
Stage IIA	T2, 3	pN0	M0				
Stage IIB	T2, 3	cN0	M0	Carcinoma of the skin of the penis			
Stage IIC	T4	N0	M0	Stage 0	Tis	N0	M0
Stage IIIA	AnyT	N1a*	M0		Ta	N0	M0
Stage IIIB	AnyT	N1b*, 2	M0	Stage I	T1a	N0	M0
Stage IV	AnyT	AnyN	M1	Stage II	T1b	N0	M0
*N1a: Microscopic metastasis (clinically occult: cN0 + pN1) N1b: Microscopic metastasis (clinically occult: cN1 + pN1)					T2	N0, 1	M0
					T3	N0	M0
Carcinoma of the skin of the eyelid				Stage IIIA	T1, 2, 3	N1	M0
Stage 0	Tis	N0	M0	Stage IIIB	T1, 2, 3	N2	M0
Stage IA	T1	N0	M0	Stage IV	T4	AnyN	M0
Stage IB	T2a*	N0	M0		AnyT	N3	M0
Stage IC	T2b*	N0	M0		AnyT	AnyN	M1
Stage II	T3a*	N0	M0	Soft-tissue sarcoma			
Stage IIIA	T3b*	N0	M0	Stage IA	T1a	N0	M0
Stage IIIB	AnyT	N1	M0		T1b	N0	M0
Stage IIIC	T4	N1	M0	Stage IB	T2a	N0	M0
Stage IV	AnyT	AnyN	M1		T2b	N0	M0
T2a: >5–10 mm in its greatest dimension or located at the tarsal plate or lid margin T2b: >10–20 mm in its greatest dimension or located in the full-thickness eyelid T3a: >20 mm in its greatest dimension, located in adjacent ocular/orbital structures, or showing perineural invasion T3b: Needs enucleation, exenteration, or bone resection				Stage IIA	T1a	N0	M0
					T1b	N0	N0
				Stage IIB	T2a	N0	M0
				Stage III	T2b	N0	M0
				Stage IV	AnyT	N1	M0
					AnyT	AnyN	M1
				*Extraskeletal Ewing and primitive neuroectodermal tumors are classified as high-grade. If grade cannot be assessed, classify the tumor as low-grade.			

(Modified from Sobin LH, Gospodarowicz MK, Wittekind C (eds). *TNM Classification of Malignant Tumours (UICC: Union for International Cancer Control)*, 7th edn. Chichester: Wiley-Blackwell; 2009; and Wittekind CF, Greene FL, Hutter RVP, et al (eds). *TNM Atlas: Illustrated Guide to the TNM/pTNM Classification of Malignant Tumours*, 5th edn. Springer; 2004.)

BOX 28.4 Recommended surgical margins of wide excisions of nonmelanocytic tumors of the skin and soft tissues**Horizontal margin**

Basal cell carcinoma

low risk: 4 mm

high risk: 5–10 mm

Squamous cell carcinoma

low risk: 4–6 mm

high risk: 10 mm

Merkel cell carcinoma

10–20 mm

Sarcoma

low risk: 10 mm

high risk: 20 mm

Vertical margin**With fat layer**

Tumors that are limited to the dermis

With deep fascia

Tumors that extend into the fat layer

With skeletal muscle

Tumors that extend into the deep fascia

With the membranes of deeper structures such as cartilage or bone

Tumors that extend into skeletal muscle

With deeper structures like cartilage or bone

Tumors that extend into membranes of deeper structures like cartilage or bone

Others

The margins of wide tumor excisions that occur in anatomically complicated and special regions (e.g., eyelid, vulva, penis, finger/toe tip, and ear) will vary on a case-by-case basis. This is also true for soft-tissue tumors. In general, at least one layer of barrier structure should be excised. For example, for tumors that are limited to the fat layer, the deep fascia of skeletal muscle is considered as the barrier structure and should be removed with the tumor upon wide excision.

chemotherapy that malignant skin tumors are generally treated with can sometimes be seen as neoadjuvant chemotherapy before surgery for advanced stage cancer. Single-agent chemotherapies include peplomycin sulfate and CPT-11¹⁸ for SCC, paclitaxel for angiosarcoma, and docetaxel for angiosarcoma and EMPD. Multiagent chemotherapies includes cisplatin + doxorubicin and cisplatin + 5-fluorouracil (5-FU) + bleomycin for SCC; mesna + doxorubicin + ifosfamide + dacarbazine for angiosarcoma; and 5-FU + mitomycin C, 5-FU + carboplatin + leucovorin, and 5-FU + carboplatin + mitomycin C + epirubicin + vincristine for EMPD.

Laser therapy

Dye lasers or neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers can be used for lesions that are characterized by neoplastic changes or malformations in capillary vessels or

their overgrowth, such as hemangiomas,¹⁹ vascular malformations,²⁰ and keloid/hypertrophic scars.²¹ Ruby and alexandrite lasers can be used to treat superficial pigmented lesions whose colors range from brown to black, while Q-switched ruby and alexandrite lasers are useful for intradermal pigmented lesions such as the nevus of Ota.²² CO₂ lasers and erbium yttrium aluminum garnet (Er:YAG) lasers target the water content of a lesion,²³ which makes them suitable for lesions with various colors like seborrheic keratosis, telangiectatic granuloma, xanthoma, and fibroma.

Others (including immunotherapy, cryotherapy, electrocoagulation therapy, and sclerotherapy)

At this stage, the only indication for immunotherapy is malignant melanoma. Cryotherapy and electrocoagulation therapy induce the freezing and melting of the tumor tissues, which results in their necrosis and/or apoptosis; these methods are suitable for superficial benign or malignant tumors like seborrheic keratosis, fibroma, and BCC. Sclerotherapy, where a sclerosant like ethanol, ethanolamine oleate, polidocanol, or OK-432 is injected into affected vessels, can be used to treat vascular malformations. Promising technologies that may become useful in the near future include: hyperthermic infusion therapy, where the tumor is infused with a substance that makes it more susceptible to locally applied heat; molecular target therapy, which involves drugs or other substances that block the growth and spread of the tumor by interfering with specific tumor growth and progression molecules; and gene therapy and gene cell therapy, where genes are manipulated in target healthy cells (to enhance their cancer-fighting properties) or in target cancer cells (to kill them or inhibit their growth).

Benign cutaneous and soft-tissue tumors**Benign epithelial-origin tumors***Epidermal nevus (e.g., verrucous epidermal nevus and linear epidermal nevus)*

This nevus is composed of skin cells that normally occur at the affected site but show hyperkeratosis and papillomatosis (Fig. 28.7). It can be considered to be a hamartoma, which is a benign focal, tumor-like malformation that is composed of a mixture of the cells that characterize the tissue of its origin;



Fig. 28.7 Epidermal nevus of the upper arm.

such nodules grow at the same rate as the surrounding tissues. The dermis below the epithelial nevus is usually normal. Epithelial nevi sometimes exhibit a diffuse or extensive distribution that affects a large area of the patient's body (termed systematized epidermal nevus); careful observation is necessary in these cases. Systematized epidermal nevus often occurs together with abnormalities in other organ systems. This condition is termed epidermal nevus syndrome,²⁴ and has been described as a sporadic neurocutaneous linkage of congenital ectodermal defects in the skin, brain, eyes, and/or skeleton. Laser therapy, cryotherapy, electrocoagulation, surgical abrasion, and excision are suitable for treating epithelial nevi. If abrasion therapy is used, it should be remembered that these lesions are usually limited to the epidermis; thus, to prevent heavy scarring, only the epidermis and the superficial layer of the dermis should be removed.

Seborrheic keratosis (also known as senile wart)

This is a benign skin growth that originates from the basal and squamous cells in the epidermis (Fig. 28.8). It should be differentiated from nevus cell nevus, senile keratosis, BCC, and malignant melanoma. The sign of Leser-Trélat, which is the dramatic, sudden appearance of multiple seborrheic keratoses, can be a paraneoplastic syndrome, namely an ominous sign of an internal malignancy.²⁵ In such cases, not only do new lesions suddenly appear, pre-existing lesions also frequently increase in size and become symptomatic. This sign should not be overlooked and screening for internal malignancy should be recommended to the patient. Laser therapy, cryotherapy, electrocoagulation, surgical abrasion, and excision are all suitable treatments for seborrheic keratosis. However, if the tumor invades the dermis, which can occur, surgical excision is recommended.

Keratoacanthoma

Keratoacanthoma has been a controversial entity for many years, mainly because it closely resembles SCC²⁶ (Fig. 28.9). It grows rapidly and can sometimes self-heal. Upon histopathology, atypical squamous cells can be detected, which makes it difficult to distinguish from SCC. For this reason, excisional biopsy should be considered despite the fact that this lesion

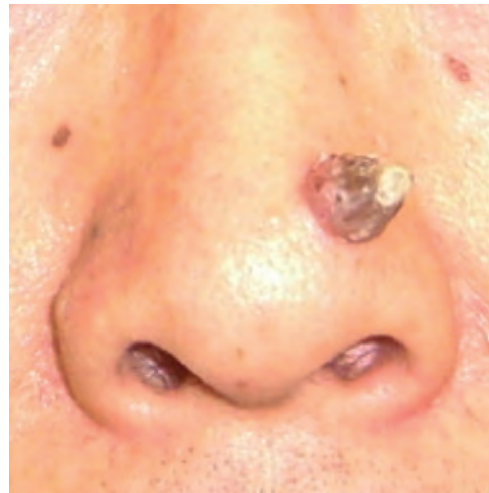


Fig. 28.9 Keratoacanthoma on the nose.

occasionally self-heals. If the lesion is on the nose and face, Mohs micrographic surgery is particularly suitable since it facilitates good margin control along with minimal tissue removal.

Epidermoid cyst (also known as epidermal cyst and atheroma)

Epidermal cyst is a smooth, dome-shaped, freely movable, somewhat fluctuant subcutaneous swelling that is sometimes attached to the skin by a central pore (Fig. 28.10). It is covered with a stratified squamous epithelium that resembles the epidermis or the follicular infundibulum; thus, there is a granular cell layer adjacent to the keratin-containing cyst lumen. Epidermoid cysts can rupture spontaneously or be ruptured by external mechanical forces. Extremely large epidermoid cysts, also known as giant atheromas (Fig. 28.11), should undergo pathology to rule out malignant change,²⁷ although such changes are rare. Epidermoid cysts that exhibit inflammation or recur should be removed by simple excision. In the case of large cysts, the contents can be removed first, after which the cyst walls can be removed with minimal



Fig. 28.8 Seborrheic keratosis on the temporal region.



Fig. 28.10 Epidermoid cyst with a central pore.



Fig. 28.11 Giant atheroma.

incision (Fig. 28.12). In cases where pus and blood are excreted, the surgeon should consider incising the cyst and draining it first, and then excising it completely 1–2 weeks later.

Milia

Milia are a smaller version of an epidermoid cyst (less than 4 mm in diameter). They may derive from the outer root sheath of vellus follicles. There are primary and secondary milia.²⁸ Primary milia include congenital milia, benign primary milia of children and adults, milia en plaque, nodular grouped milia, multiple eruptive milia, nevus depigmentosus with milia, and genodermatosis-associated milia. Secondary milia are the disease-, medication-, and trauma-associated milia. Milia can be treated easily by making small holes in the surface with a needle or CO₂ laser and then extruding the contents.

Dermoid cyst

A dermoid cyst is a congenital subcutaneous cyst that develops along the embryonic lines of closure (Fig. 28.13). It is most common on the head and neck area, particularly the supraorbital region, brow, upper eyelid, glabella, and scalp. These cysts can be easily removed surgically, but care should be taken not to injure the temporal branch of the facial nerve. The cyst lumen contains keratin debris and hair shaft fragments. Preoperative X-rays should be taken to distinguish it

from pilomatricoma on the head and neck region, especially in pediatric patients. Since it has been reported that dermoid cysts can exhibit malignant changes, complete surgical removal is recommended.²⁹

Others

Rare benign epidermal-origin skin tumors include clear cell acanthoma, large cell acanthoma, acantholytic acanthoma, warty dyskeratoma, traumatic inclusion cyst, human papillomavirus-associated cyst, proliferating epidermal cyst, and cutaneous keratocyst. The preoperative diagnosis of these tumors can be difficult, but many can be treated radically with a simple excision and suture.

Benign appendage-origin tumors

Nevus sebaceus

Nevus sebaceus is a hamartoma rather than a neoplasm (Fig. 28.14). It is essentially confined to the head and neck regions, and can be found not only in the sebaceous gland but also in the epidermis, dermis, hair follicles, and sweat glands. Consequently, it is also referred to as organoid nevus. In appearance, it resembles an epidermal nevus. Since other tumors such as BCC and trichilemmoma can arise from nevus sebaceus over time,³⁰ complete surgical excision is recommended. If it is located in the hair, the hair stream should be carefully considered while performing the excision and suturing; moreover, dehairing caused by unnecessary buried or dermal sutures should be avoided.

Pilomatricoma (also known as calcifying epithelioma and pilomatrixoma)

This is a cystic nodule that tends to occur on the head and neck regions of young patients (Fig. 28.15). Multiple pilomatricoma may be seen in a familial setting in patients who also have myotonic dystrophy. A calcified region can be seen by ultrasound, X-ray, CT and MRI. This region will appear as a high-intensity signal on ultrasound, while on MRI it will show up as a low-intensity signal on both T1WI and T2WI. Since malignant tumors sometimes have a calcified lesion that is caused by necrosis, it is necessary to exclude this possibility when making a diagnosis of pilomatricoma. It is not associated with a clear capsule and thus should be excised carefully and completely to prevent recurrence. Malignant



Fig. 28.12 An epidermoid cyst (A) and the removal of the cyst with a minimal incision (B, C).

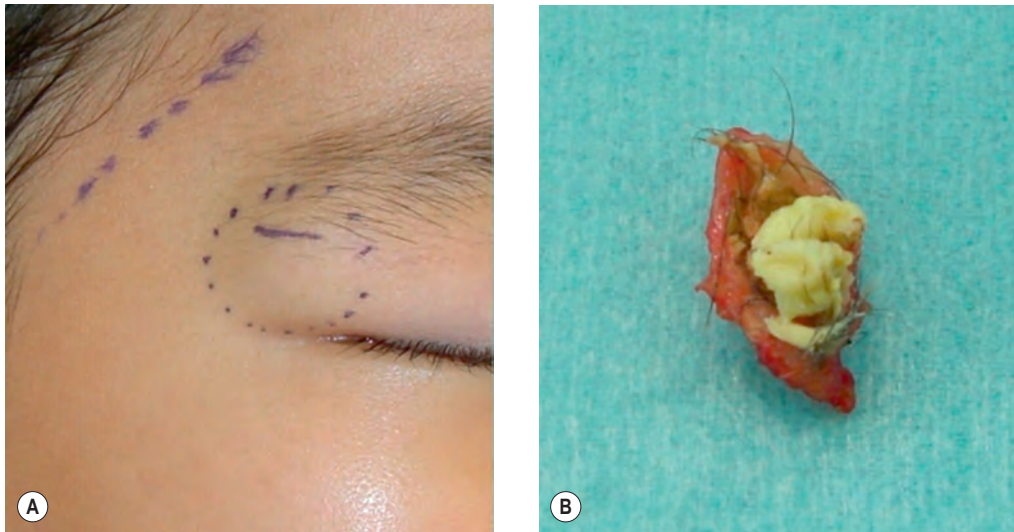


Fig. 28.13 (A) Dermoid cyst on the supraorbital region. (B) The excised cyst.

pilomatricoma has been reported,³¹ but there have been less convincing reports of the carcinomatous transformation of pre-existing benign pilomatricoma.

Trichilemmal cyst

This is a subcutaneous cyst that is derived from the outer root sheath of the hair follicle and arises most frequently on the hairy region on the head (Fig. 28.16). Clinically, it resembles an epidermoid cyst. Multiple cysts on the head are seen in 70% of cases. Complete excision is recommended. The conservative approach involves a small punch biopsy of the cyst that allows the cyst cavity to be entered. The contents of the cyst can then be emptied, leaving an empty cyst wall that can be grasped with a forceps and pulled out of the small incision. This method often results in a very small scar and very little, if any, bleeding. Proliferating trichilemmal cyst is an uncommon lesion that is characterized histologically by trichilemmal keratinization. It is thought to originate from a trichilemmal cyst and to have the potential for malignant transformation, at which point it is termed a malignant proliferating trichilemmal cyst.³²

Syringoma

Syringoma is the result of intradermal eccrine proliferation that is malformative rather than neoplastic in most cases. It

occurs mainly on the eyelids and presents as a 1–2-mm nodule. Since the main reason for treating syringoma is cosmetic, the tumor should be destroyed in such a way that there is minimal scarring and no recurrence. For this purpose, electrocoagulation, dermabrasion, CO₂ lasers, Er:YAG lasers, and fractional photothermolysis³³ can be used, although attention should be paid to preventing pigmentation and scarring.

Apocrine cystadenoma (also known as apocrine cysthidroma)

Apocrine cystadenoma is characterized by the dilatation of an apocrine duct and secondary proliferation of the ductal epithelium that is architecturally bland (Fig. 28.17). Apocrine cystadenomas appear most commonly as solitary, soft, dome-shaped, and translucent papules or nodules. They are located most frequently on the eyelids, especially the inner canthus. They grow slowly and usually persist indefinitely. They can be incised and drained, but electrosurgical destruction of the cyst wall is often needed to prevent recurrence. Punch, scissors, or elliptical excision



Fig. 28.14 Nevus sebaceus on the scalp.

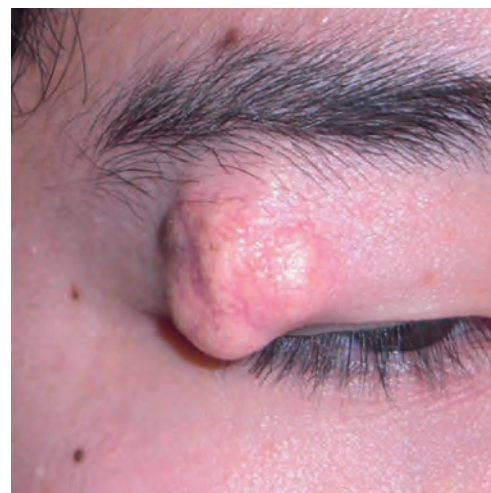


Fig. 28.15 Pilomatricoma on the upper eyelid.

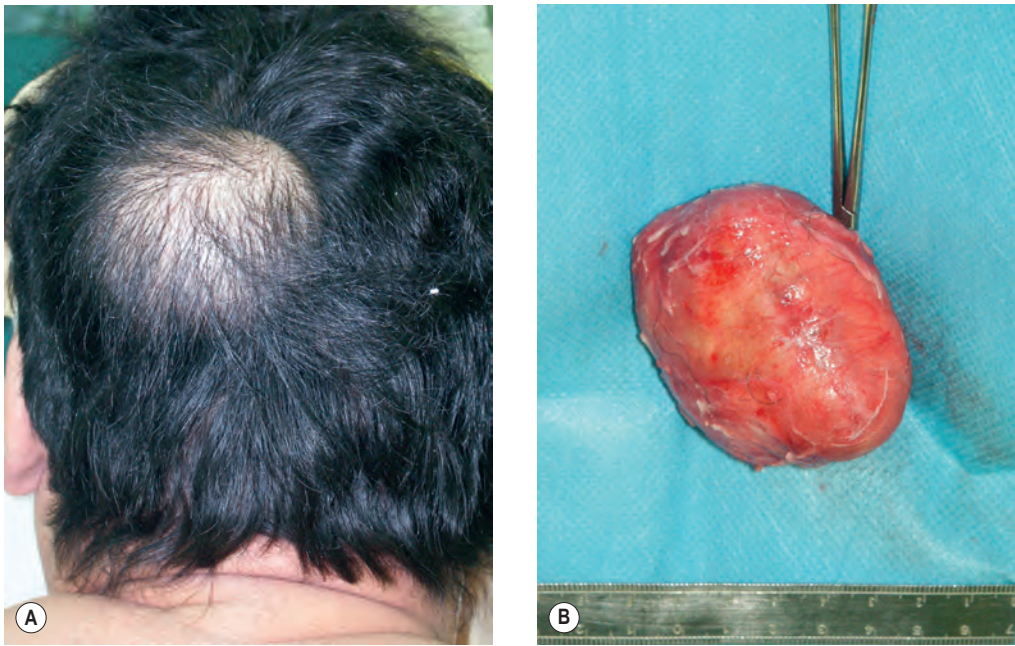


Fig. 28.16 Solitary trichilemmal cyst on the scalp (A) and after its excision (B).

can also remove these tumors. Multiple cystadenomas can be treated with a CO₂ laser. Trichloroacetic acid³⁴ has also been used.

Chondroid syringoma (also known as cutaneous mixed tumor)

Chondroid syringoma derives from the sweat glands and is most frequently seen on the head and neck, where it presents as an unexceptional dermal or subcutaneous nodule (Fig. 28.18). The tumor consists of a gland-like epithelial component that is set in a chondromyxoid stromal component. It is believed that there are both eccrine and apocrine variants. Hirsch and Helwig proposed the following five histologic criteria for diagnosis: (1) nests of cuboidal or polygonal cells; (2) intercommunicating tubuloalveolar structures lined with

two or more rows of cuboidal cells; (3) ductal structures composed of one or two rows of cuboidal cells; (4) occasional keratinous cyst; and (5) a matrix of varying composition. Since malignant forms have been reported, although they are rare, complete surgical excision is recommended.³⁵

Others

Other benign appendage-origin tumors include steatocystoma multiplex (Fig. 28.19), trichofolliculoma, trichoepithelioma, poroma folliculare, trichilemmoma, sebaceous adenoma, eccrine nevus, and apocrine nevus. Moreover, hair follicles, sebaceous glands, and sweat glands (apocrine and eccrine glands) can undergo hyperplasia that results in a hamartoma; these skin appendages can also develop adenomas, benign epitheliomas, and primordial epitheliomas.



Fig. 28.17 Apocrine cystadenoma on the earlobe.

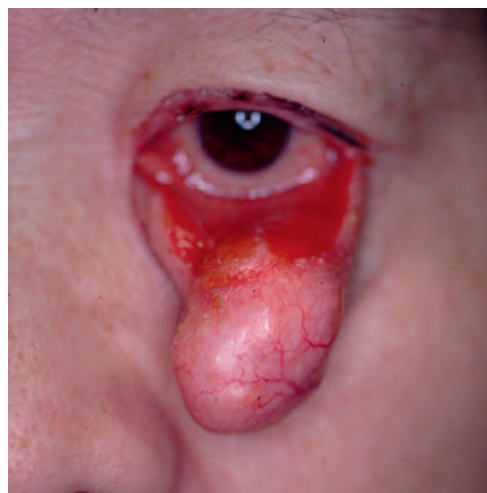


Fig. 28.18 Chondroid syringoma on the lower eyelid.



Fig. 28.19 Steatocystoma multiplex on the trunk.



Fig. 28.20 Lentigo simplex on the forearm.

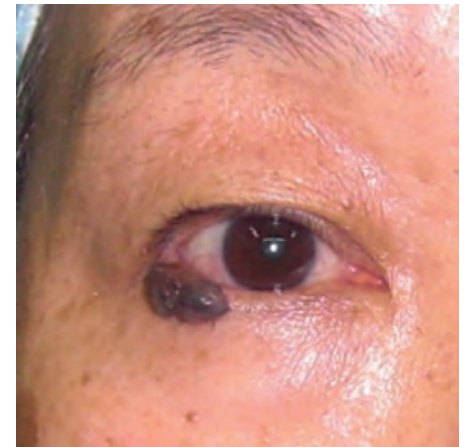


Fig. 28.21 Intradermal nevus on the lower eyelid.

Benign neural crest-origin tumors

Pigment cell nevus (also known as pigmented nevus and nevus cell nevus)

These are acquired and congenital nevi that originate from melanocytes. It has been suggested that healthy adults have on average 5–10 nevi. Dome-like elevated nevi sometimes bear hair. If an acquired nevus has a diameter of more than 7 mm and it is still growing, the possibility of malignant melanoma should be considered. It seems now that malignant melanomas do not originate from pigment cell nevus (except in the case of congenital giant nevus) but rather derive directly from epidermal melanocytes; this is known as the *de novo* carcinogenesis theory.³⁶ There are five types of pigmented nevi, as follows.

Lentigo simplex

Lentigo simplex is a black–brown pigmented nevus, 2–3 mm in diameter. It is believed to be an acquired pigment cell nevus that is at an early stage (Fig. 28.20). Its margins can be either jagged or smooth. It is the result of the proliferation of melanocytes in the basal layer of epidermis. It is not induced by sun exposure and is not associated with systemic disease. The lesions are few in number and may occur anywhere on the skin or mucous membranes. They usually first appear in early childhood around 3 years of age, but they can also be present at birth or develop later. Cryosurgery, lasers,³⁷ and simple excision can be tried.

Acquired pigment cell nevus

Acquired pigment cell nevi are due to the proliferation of melanocytes and can be divided into three types according to the location of the melanocytes. In junction nevi, the melanocytes are mainly located at the junction between the epidermis and dermis. In compound nevi, the melanocytes are located in the dermis as well as at the junction between the epidermis and dermis. In intradermal nevi (Fig. 28.21), the melanocytes are in the dermis only. Laser treatment is ineffective for melanocytes located in the deeper layer of dermis because these cells lack the melanin pigment. Thus, simple surgical excision is recommended to prevent recurrence. The nevus

that has a depigmented area around it is called Sutton's halo nevus.³⁸

Congenital pigment cell nevus

The congenital pigment cell nevus is present at the time of birth and increases in size as the body grows, although its shape does not change. It is classified according to size into the small type (less than 1.5 cm in diameter), medium type (1.5–20 cm in diameter), and large or giant type (over 20 cm in diameter) (Fig. 28.22). Histology shows that the nevus cells tend to be diffusely distributed in the deep layer of the dermis. Careful observation is needed because malignant melanomas can arise from giant congenital pigmented cell nevi.³⁹ Nevi that present on both the upper and lower eyelids are called divided nevi, while hairy giant nevi are called animal-skin nevi (Fig. 28.23). Giant nevi should be removed and reconstructed by the serial excision method, skin grafting, local flaps, or a combination of these.

Dysplastic nevus (also known as Clark's nevus and atypical mole)

Clinically, dysplastic nevus resembles an early-stage malignant melanoma.⁴⁰ It was initially thought to be a prodrome of



Fig. 28.22 Medium-type congenital pigment cell nevus on the shoulder.



Fig. 28.23 Animal-skin nevus.

malignant melanoma but is now suggested to be a type of acquired pigment cell nevus. Complete excision and pathologic examination should be performed. The US National Institutes of Health Consensus Conference on the diagnosis and treatment of early melanoma defined the familial atypical mole and melanoma syndrome,⁴¹ the criteria for which are the occurrence of malignant melanoma in one or more first- or second-degree relatives, the presence of numerous (often >50) melanocytic nevi, some of which are clinically atypical, and the presence of certain histologic features in many of the associated nevi.

Juvenile melanoma (also known as Spitz nevus)

This is a dome-like nodule that is about 1 cm in diameter and occurs on the face or legs of young patients (Fig. 28.24).⁴² The surface is smooth and sometimes exhibits telangiectasia. It may be nonpigmented or have a color that ranges from pink to orange-red. Some lesions are pigmented, especially those on the lower extremities. After its appearance, the lesion tends

to grow rapidly and may reach a size of 1 cm within 6 months. After this rapid initial growth phase it tends to become static, although color changes may be observed. Bleeding and pruritus are rare. Complete excision and pathologic examination should be performed.

Nevus spilus (also known as café-au-lait spot)

This is a benign tumor of melanocytes that is characterized by the increased accumulation of melanin granules rather than the proliferation of melanocytes (Fig. 28.25). The whole nevus has a uniform café-au-lait color. The presence of six or more nevus spilus lesions that are greater than 5 mm in diameter in prepuberty and over 15 mm in diameter in postpuberty is indicative of neurofibromatosis type 1 (NF1), also known as von Recklinghausen's disease (Fig. 28.26). NF1 is caused by a mutation of the chromosome band 17q11.2, which encodes neurofibromin. Neurofibromatosis type 2 (NF2) patients rarely have nevus spilus lesions and do not demonstrate the cutaneous neurofibromas that typically result in the early diagnosis of NF1, although they may have cutaneous schwannomas that resemble skin tags. Moreover, because symptoms from cranial nerve VIII schwannomas usually begin in the third decade of life, patients with NF2 are typically diagnosed later in life than patients with NF1.⁴³

Becker's melanosis (also known as Becker's pigmented hairy nevus)

This lesion is characterized by the slight proliferation of melanocytes in the basal layer of the epidermis, the increasing accumulation of melanin granules, and the presence of hair. It mainly occurs in males and develops at puberty, which suggests that androgens may play a role in its development. This is supported by the fact that it is associated with hypertrichosis, the occasional development of acneiform lesions within the patch, and, albeit rarely, with an accessory scrotum in the genital region. In addition, it has been reported that Becker melanosis lesional skin has significantly more androgen receptors than the normal surrounding skin. Ruby lasers, CO₂ lasers, and Er:YAG lasers can be used to treat Becker's melanosis.⁴⁴



Fig. 28.24 Spitz nevus on the cheek.



Fig. 28.25 Solitary nevus spilus on the knee.



Fig. 28.26 Nevus spilus on the thigh of patient with neurofibromatosis type 1.

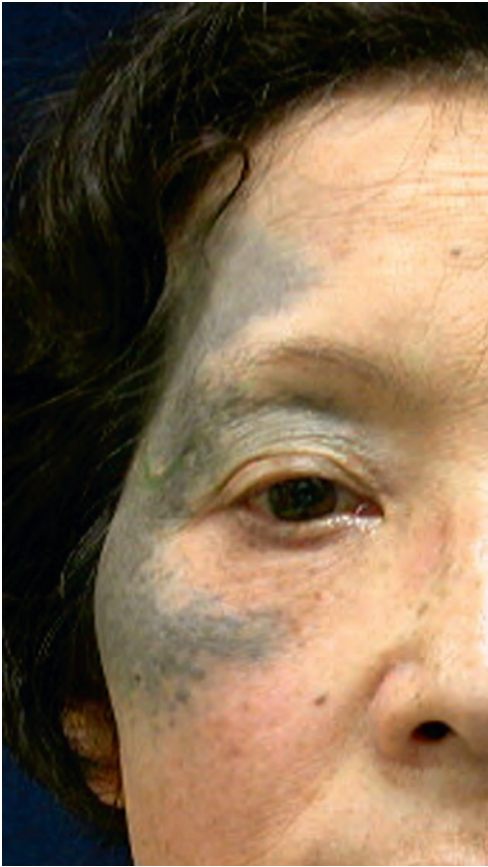


Fig. 28.27 Nevus of Ota.

Nevus of Ota (also known as nevus fuscoceruleus ophthalmomaxillaris and oculodermal melanocytosis)

This is a blue nevus that arises from the first and second branches of the trigeminal nerve (Fig. 28.27). It is common in Asians and rare in Caucasians. Women are nearly five times more likely to be affected than men. It is not congenital but appears during early infancy and puberty.⁴⁵ It is caused by the proliferation of melanocytes in the dermis. Bilateral nevus of Ota also exists: this is called acquired bilateral nevus of Ota-like macules or late-onset dermal melanocytosis. It has been suggested that nevus of Ota may be derived from melanocytes that have not migrated completely from the neural crest to the epidermis during embryogenesis. The variable prevalence among different populations suggests a genetic influence, but familial cases of nevus of Ota are exceedingly rare. The two peak ages of onset in early infancy and early adolescence suggest that hormones are a factor in the development of this condition. Q-switched ruby or alexandrite lasers have been used to treat nevus of Ota.⁴⁶ After 4–8 treatments, the degree of skin pigmentation is reduced dramatically. Cryotherapy, dermabrasion, or peeling can also be used as a multimodal therapy on a case-by-case basis.

Nevus of Ito

This dermal melanocytosis can be considered as a subtype of nevus of Ota (Fig. 28.28). It occurs on the acromiodeltoid

region.⁴⁷ Its pathogenesis is unclear, but the fact that the dermal melanocytes of the nevus of Ito are in close proximity with nerve bundles suggests the nervous system may be a factor in its development. Recommended treatments are the same as those for nevus of Ota.

Mongolian spot (also known as congenital dermal melanocytosis)

More than 90% of Native American, 80% of Asian, and 70% of Hispanic infants have this proliferative disorder of dermal melanocytes, which presents as bluish-gray spots on the sacral and coccygeal region (Fig. 28.29). Fewer than 10% of Caucasian infants have Mongolian spots. These spots disappear before the age of 10 years. The blue-gray color is due to the melanocytes that are deep in the skin. It usually presents as multiple spots or one large patch covering the lumbosacral area (lower back), buttocks, flanks, and/or shoulders (Fig. 28.30). It results from the entrapment of melanocytes in the dermis during their migration from the neural crest to the epidermis during embryonic development.⁴⁸ Treatment is usually not necessary, but Q-switched alexandrite laser can be used for severe cases.

Blue nevus

Like the nevus of Ota and the Mongolian spot, this is a dermal melanocytosis. However, it involves more cells, which means it has a nodular form. There are three types: common, cellular, and combined.⁴⁹ The cellular lesion is usually larger than the common lesion and tends to invade the subcutaneous tissue. The combined lesion is a blue nevus that is combined with a pigment cell nevus or a juvenile melanoma. A biopsy should be performed to determine the proper diagnosis. For a solitary lesion, simple excision is usually curative. There are rare cases of persistent blue nevi that manifest as satellite lesions around the original excision site. These must be distinguished from malignant blue nevus and re-excision is recommended.



Fig. 28.28 Nevus of Ito.

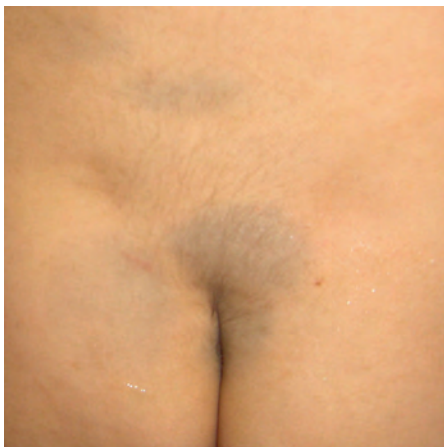


Fig. 28.29 Typical Mongolian spot on an Asian infant.



Fig. 28.30 Atypical Mongolian spot on the back.

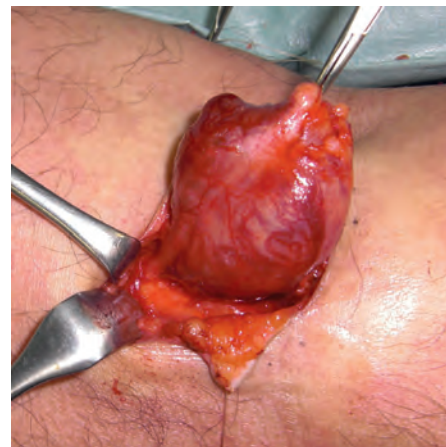


Fig. 28.31 Schwannoma on the popliteal region.

Neuroma

Neuromas are hamartomas composed of peripheral nerve components, namely Schwann cells, fibroblasts, and axons; they arise as a result of ineffective, unregulated nerve regeneration that leads to neurofiber hyperplasia. They are often the result of nerve injury, especially injuries sustained during surgery; both superficial (skin or subcutaneous fat) and deep (e.g., cholecystectomy) surgery can induce neuromas. Neuromas are often very painful. It should be noted that neuroma is often used as a general term to describe any swelling of a nerve; thus, it does not necessarily mean neoplastic tumors. An example of this more general usage of the term is Morton's neuroma, which is a mononeuropathy of the foot; to avoid confusing it with a tumor, this condition is now often referred to as Morton's metatarsalgia.⁵⁰ Surgical removal is the treatment of choice for neuromas.

Schwannoma (also known as neurilemmoma)

This is a benign proliferation of Schwann cells in the dermis or subcutaneous tissues (Fig. 28.31). NF2 is associated with multiple schwannomas. Pathology shows that there are two basic histological types of schwannoma called Antoni types A and B. Type A is characterized by numerous Verocay bodies. These are acellular, eosinophilic areas that are oval, linear, or serpiginous in shape and are surrounded by parallel-lying or palisading bundles of spindled Schwann cells with blunt, elongated nuclei. In each Verocay body, the long axes of the cells are all oriented toward the acellular area. Type B lacks Verocay bodies and consists of a loose, myxomatous stroma with fewer and more randomly arranged spindle cells. Neither type appears to have neurites. Schwannomas are typically encapsulated and the associated peripheral nerve may be seen in the microscopic section. Occasionally, older lesions show degenerative changes such as hemorrhage, hemosiderin deposition, mild chronic inflammatory cell infiltration, dense fibrosis, and nuclear pleomorphism. Such ancient schwannomas⁵¹ are benign but must be differentiated from neurofibrosarcoma and malignant schwannoma. Surgical removal is the first choice of treatment.

Neurofibroma

A neurofibroma is a benign tumor of the peripheral nerve sheath. It is usually found in individuals with the genetically inherited diseases NF1 and NF2, and can result in symptoms that range from physical disfiguration and pain to cognitive disability (Figs. 28.32 & 28.33). Neurofibromas arise from Schwann cells but also incorporate many other types of cells and structural elements, which makes it difficult to identify and understand all the pathogenic mechanisms. Neurofibromas should be removed surgically or treated with a CO₂ laser. However, once a plexiform neurofibroma⁵² has undergone malignant transformation, radiation and chemotherapy can be used as adjuvant therapies.

Others

Other benign neural crest-origin tumors include the granular cell tumor and rudimentary polydactyly. The latter often have normal Merkel cells in the basal portion of the epidermis in addition to the proliferation of nerve fibers and encapsulated corpuscles. The proliferation of various neural components may be the essential feature of this condition.



Fig. 28.32 Mild neurofibroma on a patient with neurofibromatosis type 1.



Fig. 28.33 Severe neurofibroma on a patient with neurofibromatosis type 1.

Benign mesenchymal-origin tumors

Dermatofibroma (also known as fibrous histiocyoma)

Dermatofibroma is a common cutaneous nodule that frequently develops on the extremities (mostly the lower legs). It is usually asymptomatic, although pruritus and tenderness are not uncommon. It is characterized by the proliferation in the dermis of both fibroblasts and other cell types, including histiocytes (skin macrophages) and vascular endothelial cells. It can be divided into the cellular type, which is mainly characterized by histiocyte proliferation, and the fibrous type, which predominantly shows fibroblast proliferation. Strong endothelial cell proliferation can sometimes be observed in both types, in which case a diagnosis of sclerosing hemangioma is made (Fig. 28.34). Moreover, if the cellular components are small and the tumor is composed of hyalinized collagenous fibers, it can be called a sclerotic fibroma. There are many other special dermatofibroma forms, including hemosiderotic histiocyoma, xanthomatous histiocyoma, atypical

dermatofibroma, aneurysmal dermatofibroma, myxoid dermatofibroma, and keloidal dermatofibroma.⁵³ Removal of the tumor is not necessary unless diagnostic uncertainty exists or particularly troubling symptoms are present.

Xanthoma

Xanthoma is characterized by the aggregation of foamy histiocytes that have phagocytized lipids (Fig. 28.35). The most common xanthoma occurs on the upper eyelid and is often associated with hyperlipidemia. Xanthomas are not always associated with underlying hyperlipidemia but when they are, it is necessary to diagnose and treat the underlying lipid disorders to decrease the xanthoma size and reduce the risk of atherosclerosis. Treatment of the hyperlipidemia initially entails dietary changes and the use of lipid-lowering agents such as statins, fibrates, bile acid-binding resins, probucol, or nicotinic acid. Eruptive xanthomas usually resolve within weeks of initiating systemic treatment, while tuberous xanthomas usually resolve after a few months. However, tendinous xanthomas take years to resolve or may persist indefinitely. While the main goal of therapy for hyperlipidemia is to reduce the risk of atherosclerotic cardiovascular disease, in patients with severe hypertriglyceridemia the goal is to prevent pancreatitis. Surgery or locally destructive modalities, including lasers, can be used for idiopathic or unresponsive xanthomas.⁵⁴

Juvenile xanthogranuloma

This is a single or multiple dome-like tumor that occurs on the head and neck region, the body, or the limbs of young patients. Approximately 35% of cases of juvenile xanthogranuloma occur at birth, with as many as 70% of cases occurring in the first year. Most juvenile xanthogranulomas resolve by the age of 5 years. Despite the term “juvenile” in the disease name, 10% of cases manifest in adulthood (Fig. 28.36). Histologic analysis can reveal the presence of Touton giant cells (Fig. 28.37). This tumor can be associated with NF1, Niemann–Pick disease, urticaria pigmentosa, and juvenile chronic myelomonocytic leukemia.⁵⁵ The lesions can be excised for diagnostic and cosmetic reasons.



Fig. 28.34 Sclerosing hemangioma.

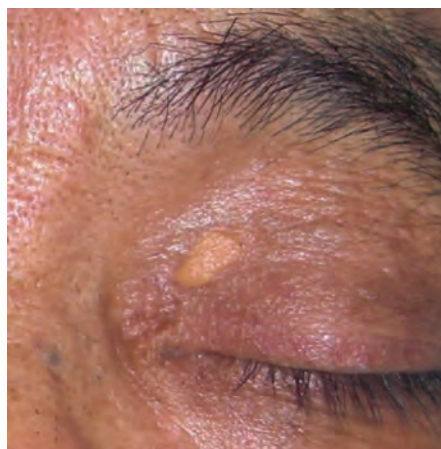


Fig. 28.35 Xanthoma on the upper eyelid.



Fig. 28.36 An adult-onset juvenile xanthogranuloma on the elbow.

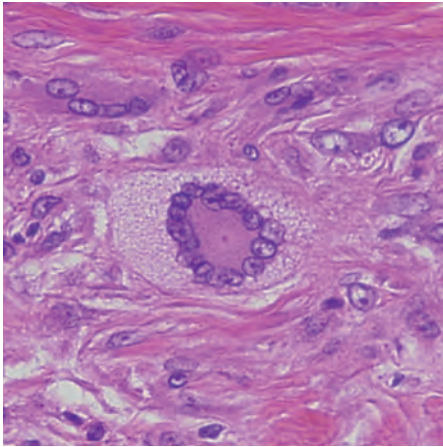


Fig. 28.37 Touton giant cell in a juvenile xanthogranuloma.



Fig. 28.38 Acrochordon.



Fig. 28.39 Fibroma pendulum.

Soft fibroma

There are three types of soft fibroma: (1) acrochordon (also known as a skin tag) (Fig. 28.38), which occurs on the neck and axilla and increases after middle age; (2) fibroma pendulum⁵⁶ (Fig. 28.39), which is a large fibroma over 10 mm in diameter that has a narrow pedicle; and (3) any but (1) and (2). The color can vary between normal skin color and brownish-red. Small, pedunculated soft fibromas can be removed with curved or serrated blade scissors, while larger skin tags may simply require excision. For small, soft fibromas, aluminum chloride applied prior to removal will decrease the amount of bleeding, which is usually minor anyway. Anesthesia prior to electrodesiccation is another option. Other methods of removal include cryotherapy and ligation with a suture or a copper wire; however, freezing of the surrounding skin during liquid nitrogen cryotherapy may result in dyschromic lesions. Taking hold of the acrochordon with forceps and applying cryotherapy to the forceps may provide superior results.

Keloid and hypertrophic scars

These scars are caused by the hyperproduction of collagen due to abnormal and prolonged cutaneous wound healing. It has been suggested that mechanical forces such as skin-stretching tension and mechanotransduction signaling pathways are associated with their generation and growth.⁵⁷ The differential diagnosis of keloids (Fig. 28.40) and hypertrophic scars (Fig.



Fig. 28.40 Typical keloids on the anterior chest of an Asian patient.

28.41) remains difficult; indeed, it is possible that they are manifestations of a fibroproliferative disorder of the skin⁵⁸ that expresses a continuum of features. Nevertheless, for simplicity in clinical situations, the terms “hypertrophic scars” and “keloids” can still be used: hypertrophic scars are considered to be those that improve naturally and gradually, although the full maturation process may take up to 2–5 years, whereas keloids are considered to be those that rarely resolve naturally. To prevent the development of these scars and to treat them, multimodal therapy²¹ that includes steroid ointment/tape/injection, taping fixation, silicone gel sheeting, surgery, radiation,⁵⁹ cryotherapy, laser, and 5-FU is recommended.

Lipoma

Lipoma is the most common of the mesenchymal soft-tissue tumors (Figs. 28.42 & 28.43). There are many subtypes,



Fig. 28.41 Typical hypertrophic scars on the thigh of an Asian patient.

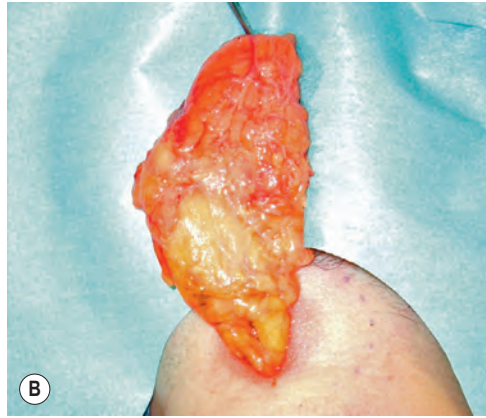


Fig. 28.42 Lipoma on the nape (A) and the lesion after excision (B).



Fig. 28.43 Lipoma on the face.

including lipoblastoma, angiolipoma, spindle cell lipoma, pleomorphic lipoma, and hibernoma. It was shown recently that these adipocellular tumors are characterized by specific chromosome and gene abnormalities and that these abnormalities can be used for diagnosis. Lipomas can be classified according to their location into entities such as intramuscular and intermuscular lipoma. Systemic lipoma is termed lipomatosis (Fig. 28.44). Diffuse lipomatosis sometimes affects the limbs, head and neck, and intestinal tract. Lipomatosis on the finger results in megadactyly. Multiple symmetric

lipomatosis⁶⁰ mainly occurs on the upper body (Fig. 28.45). Steroid-induced lipomatosis can be a side effect of corticosteroid administration. A rapidly growing lipoma should be examined carefully to eliminate the possibility that it is actually a liposarcoma. Complete surgical excision with the capsule is advocated to prevent local recurrence.

Leiomyoma

Cutaneous or subcutaneous leiomyoma is a tumor that is derived from smooth muscles in the skin, including the arrector muscle of hair and vascular smooth muscle.⁶¹ These tumors are localized and are associated with pain. Leiomyomas can be categorized into four types: (1) multiple piloleiomyoma; (2) solitary piloleiomyoma; (3) angioleiomyoma; and (4) genital leiomyoma. Angioleiomyomas and genital leiomyomas usually occur as solitary lesions. In contrast, piloleiomyomas may be solitary or multiple; in the latter case, there may be thousands of lesions. This is because the arrector pili muscle from which piloleiomyomas originate has multiple points of insertion, such as those located proximal to the hair follicle, those located distal to the multiple attachment points within the papillary and reticular dermis, and those located in the basement membrane. Piloleiomyomas can emerge from each of these insertion points, thus occurring as multiple



Fig. 28.44 Multiple lipomatosis (A) and the lesions after excision (B).



Fig. 28.45 Multiple symmetric lipomatosis.

tumors. Angioleiomyoma often occurs on the distal area of the limbs, especially under the knee in women. In contrast, angiolipoma commonly occurs on the head in men and is often not associated with pain. Surgical excision or ablation of the leiomyoma may be helpful for some symptomatic individuals.

Rhabdomyoma

Rhabdomyoma is a benign tumor of striated muscle. It is most commonly associated with the heart and tongue but can also occasionally occur as a superficial mesenchymal tumor. There are adult, fetal, and genital types. The adult-onset type often occurs on the head and neck area, whereas the fetal type often occurs on the postauricular area of children under the age of 3 years. Patients with adult rhabdomyoma should have surgical resection of head and neck lesions, especially those lesions that compress or displace the tongue, or protrude and partially obstruct the pharynx or larynx. Fetal rhabdomyomas are usually located in the subcutaneous tissues.⁶² In most instances, they can be excised without much difficulty. Local excision is the treatment of choice for genital rhabdomyomas.

Osteochondrogenic tumors

Chondromas and osteochondromas often occur in adults on the hand and foot. Osteochondromas are sometimes associated with calcification. Osteomas are composed of mature

bone but can be considered to be reactive outgrowths. Osteoma cutis⁶³ refers to the presence of bone within the skin in the absence of a pre-existing or associated lesion, as opposed to secondary types of cutaneous ossification that are the result of metaplastic reactions to inflammation, trauma, and neoplastic processes. Osteoma cutis can be removed by excision or laser resurfacing that ablates the overlying skin. Myositis ossificans, panniculitis ossificans, and fibrodysplasia ossificans progressiva are also reactive ossifications. Exostosis is also considered to be a reactive osteochondrogenic disorder (Fig. 28.46). This often occurs on the cranial and subungual regions. Exostosis can be removed easily by a chisel and hammer, and its recurrence is rare.

Accessory auricle (also known as nevus cartilagineus)

This congenital nevus arises from the area between the tragus and the lateral neck (Fig. 28.47). Nevi that are near the ear are largely composed of cartilage, while nevi that are distant from the ear are mainly composed of hair follicles. Multiple accessory auricles⁶⁴ are sometimes associated with hemifacial microsomia. Surgical removal may be possible. If so, sufficient skin and cartilage should be removed so that flat and linear scars are the result rather than a dog-ear deformity.

Granuloma

Granulomas can be broadly classified as infectious (Fig. 28.48) and noninfectious. Almost all noninfectious granulomas are foreign-body granulomas; some of these are associated with a type IV allergy. There are a number of causes of foreign-body granuloma. These can be divided into endogenous causes such as uric acid salt, cholesterol, and sebum production, and exogenous causes such as materials injected for aesthetic surgery⁶⁵ (Fig. 28.49), vaccines, surgical sutures, and materials implanted by trauma (Fig. 28.50). Small pyogenic granulomas (telangiectatic granulomas) and foreign-body granulomas can be removed by surgery, but this may not be possible for large and multiple granulomas. In this case, systemic or local corticosteroid administration to reduce inflammation should be considered.

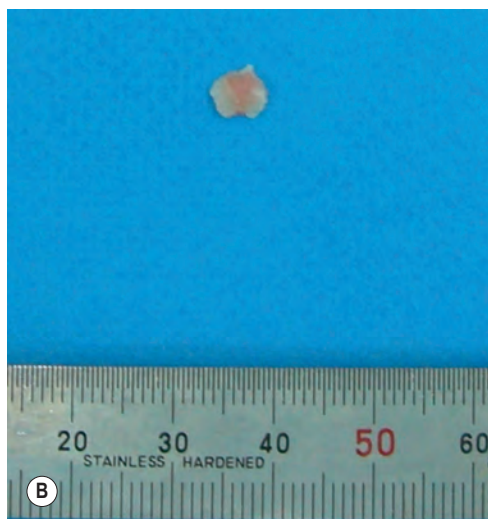


Fig. 28.46 Exostosis on the frontal bone (A) and the excised specimen (B).



Fig. 28.47 Accessory auricle.



Fig. 28.48 Pyogenic granuloma on the back.



Fig. 28.49 Foreign-body granuloma caused by a nasal implant.

Glomus tumor

Glomus tumors arise from the arterial portion of the glomus body, or the Sucquet–Hoyer canal, which is an arteriovenous anastomosis in the dermis that participates in temperature regulation. Patients with solitary glomus tumors usually have paroxysmal pain that can be severe and exacerbated by pressure or temperature changes, especially cold. Multiple glomus tumors can also be painful but are less common; the pain is also usually not severe. Two features that are useful for diagnosing glomus tumors, particularly solitary painful glomus tumors (especially those under a nail), are the Hildreth sign, which is the disappearance of pain after a tourniquet is placed on the proximal arm, and the Love test, where pain is elicited by pressing the skin overlying the tumor with the tip of a pencil. The treatment of choice for solitary glomus tumors is surgical excision. For multiple glomus tumors,⁶⁶ excision may be more difficult because of their poor circumscription and the large number of lesions. In this case, excision should be limited to symptomatic lesions.

Capillary malformation

Hemangioma simplex

This is the result of the abnormal development or differentiation of capillary vessels in the dermis.⁶⁷ According to its location, it can be classified into three types: (1) portwine stain

(face, limbs, and upper body) (Figs. 28.51 & 28.52); (2) salmon patch (medial forehead, glabella, nasal tip, and upper lip); and (3) nevus Unna (nape). Portwine stains are sometimes associated with Sturge–Weber syndrome (face) and Klippel–Trenaunay syndrome (limb). Patients with solitary hemangioma simplex, regardless of whether they have these syndromes, should be subjected to brain examinations. Of the three types, only the salmon patch can disappear within a year after birth. A dye laser or Nd:YAG laser can be used to treat these lesions.

Strawberry hemangioma

This tumor is derived from the endothelial cells of capillary vessels in the skin. It arises around 3–4 weeks after birth and its growth peaks at 6–7 months of age (Figs. 28.53 & 28.54). After this growth period, the volume rarely decreases naturally, although the color can become less livid spontaneously. Consequently, laser treatments with, for example, dye or Nd:YAG lasers should be performed at an early stage to prevent the capillaries from proliferating further.⁶⁸ On a case-by-case basis, surgical excision, steroid injection, and compression therapy may also be suitable.

Venous malformation

A representative type of venous malformation is a cavernous hemangioma, which is a blood-storing lesion with a low blood flow (Fig. 28.55). Histology shows the absence of

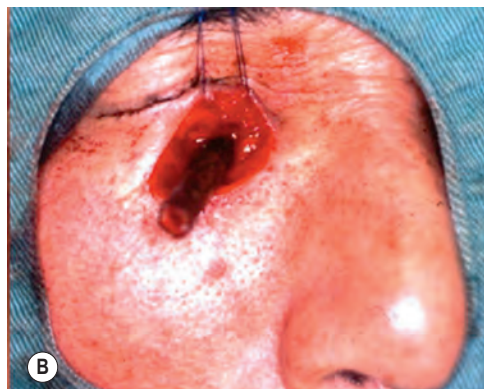
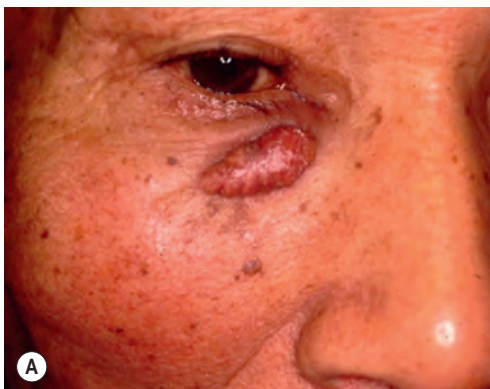


Fig. 28.50 Foreign-body granuloma caused by the implantation of a large wood splinter (A) and view of the patient just after surgery (B).



Fig. 28.51 Portwine stain on the face of an infant.



Fig. 28.52 Portwine stain on the face of an adult.

endothelial cell proliferation. It is seen in Klippel–Trenaunay syndrome, which is characterized by various malformations, including capillary malformation and bony and soft-tissue hypertrophy. Venous malformation is best treated with sclerosing therapy, where sclerosing agents like absolute ethanol, polidocanol, sodium tetradecyl sulfate, or ethanolamine oleate are injected into the lesion under ultrasound or digital subtraction angiography guidance.⁶⁹

Arteriovenous fistula and arteriovenous malformation (AVM)

Arteriovenous fistula and AVM are high-flow pulsating lesions with an arteriovenous shunt; they are either acquired because of trauma or are congenital (Fig. 28.56). CDI is useful for detecting the blood flow in the tumor. Patients with Parkes–Weber syndrome who have a huge limb AVM sometimes exhibit congestive heart failure. The Schobinger classification allows AVMs to be classified into four clinical stages: (I) quiescence; (II) expansion; (III) destruction; and (IV) decompensation. Patients with heart failure are considered to have stage IV AVMs. Surgical removal is the first choice of treatment but is often hampered by the diffuse distribution of

the vessels and the specific anatomy in the affected region (e.g., the local presence of a facial nerve). Incomplete resection results in the rapid regrowth of the remaining lesion. In cases where surgical removal is difficult, embolosclecting therapy can be used as a palliative therapy.⁷⁰

Lymphatic malformation

There are two main types of lymphatic malformation: lymphangioma and cystic hygroma. Clinically, lymphatic malformation can be classified into macrocyst (cystic hygroma and lymphangioma cystoides), microcyst (lymphangioma simplex), and combined (lymphangioma cavernous) types. The microcysts can be removed surgically, while the macrocysts and combined types should be treated by surgery or sclerotherapy using OK-432⁷¹ or absolute ethanol on a case-by-case basis.



Fig. 28.53 Strawberry hemangioma on the frontal head of an infant.



Fig. 28.54 Strawberry hemangioma on the trunk.



Fig. 28.55 Cavernous hemangioma on the lower lip.

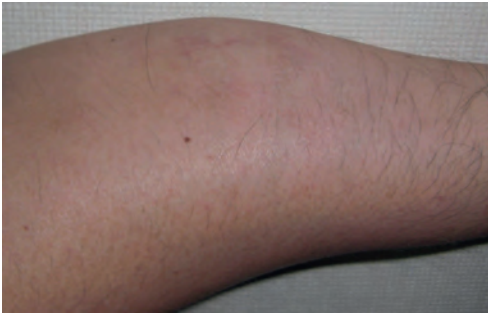


Fig. 28.56 Congenital mild arteriovenous malformation on the forearm.



Fig. 28.58 Actinic keratosis on the cheek of an elderly patient.



Fig. 28.57 Mucous cyst of the oral mucosa.



Fig. 28.59 Squamous cell carcinoma on the cheek of an elderly patient.

Others

There are many other benign mesenchymal-origin tumors. These include giant cell tumor, histiocytoma, reticulohistiocytoma, fibroxanthoma, desmoid tumor, mucous cyst of the oral mucosa (Fig. 28.57), cutaneous myxoma, Langerhans cell histiocytosis, Kimura disease, plasmacytosis, and mastocytosis.

Malignant cutaneous and soft-tissue tumors

Malignant epithelial-origin tumors

Actinic keratosis

Actinic keratosis is an intraepidermal early-stage SCC caused by long-term exposure to ultraviolet light (Fig. 28.58). It is mostly seen in the elderly, especially fair-skinned people who have been highly exposed to the sun. The areas that bear the lesions are those that have been most exposed. Over time, actinic keratoses develop into invasive SCC. They are epidermal lesions that are characterized by aggregates of atypical, pleomorphic keratinocytes at the basal layer that may extend upwards to involve the granular and cornified layers. Cutaneous horns⁷² sometimes occur in association with a

hyperkeratotic actinic keratosis. Surgical removal is recommended but cryosurgery, CO₂ lasers, 5-FU ointment, and chemical peeling may also be useful for selected cases.

Bowen's disease

Bowen's disease is an intraepidermal carcinoma since it is a malignant tumor of keratinocytes. It can progress to invasive SCC. If the invasion is deep, it is termed Bowen's carcinoma; this carcinoma can metastasize. The diagnosis of Bowen's disease is often delayed because the lesion is asymptomatic and early skin changes may be subtle and overlap with the clinical features of many conditions, including tinea corporis, nummular eczema, seborrheic keratosis, Paget's disease, superficial BCC, actinic keratosis, and psoriasis. A classic feature of the clinical history is the presentation of a nonsteroid-responsive dermatosis. Surgical removal is recommended but cryosurgery, CO₂ lasers, 5-FU ointment, and imiquimod 5% cream⁷³ may also be suitable for selected cases.

Squamous cell carcinoma

SCC is a common cutaneous malignancy that often presents as an elevated, indurated lesion with varying degrees of ulceration and crusting (Fig. 28.59). SCC can arise on any site but is most common in damaged skin such as actinically damaged skin, postburn scars (Marjolin's ulcer), traumatic



Fig. 28.60 Squamous cell carcinoma on the sole that has arisen from traumatic scars.



Fig. 28.61 Advanced squamous cell carcinoma on the face that shows necrosis and infection.

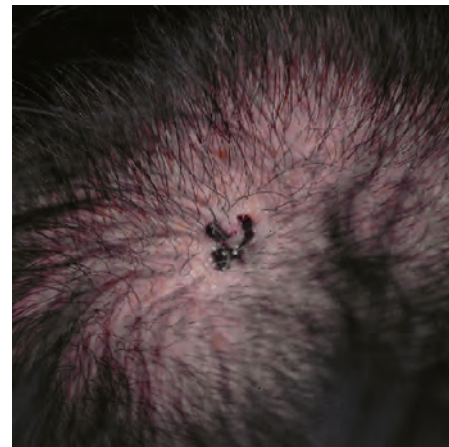


Fig. 28.62 Basal cell carcinoma on the scalp.

scars (Fig. 28.60), stasis ulcers, chronic radiation dermatitis, lupus erythematosus lesions, lichen planus on the oral mucosa, and human papillomavirus infection lesions. One type of SCC is verrucous carcinoma. Since SCC can resemble BCC, it is important to make a differential diagnosis. One notable characteristic of SCC is the bad smell caused by the macerated keratin and bacterially infected necrotic tissues (Fig. 28.61). SCC should be removed by surgery. Mohs micrographic surgery⁷⁴ is frequently used to remove SCCs. Radiotherapy given as external-beam radiotherapy or as brachytherapy (internal radiotherapy) can also be used.

Basal cell carcinoma

BCC is the most common type of skin cancer (Fig. 28.62). It rarely metastasizes and kills, but is still considered malignant

because it can invade surrounding tissues and cause significant destruction and disfigurement. It most commonly affects the head and neck, and cosmetic disfigurement is not uncommon. It can be classified into 10 types⁷⁵ (Box 28.5). It should be removed by surgery. Mohs micrographic surgery is frequently utilized. However, for selected cases of superficial BCC, CO₂ lasers or cryosurgery can be used.

Malignant appendage-origin tumors

Sebaceous carcinoma

Meibomian gland carcinoma (Fig. 28.63), Zeis gland carcinoma, and Montgomery's gland carcinoma are all sebaceous carcinomas. These carcinomas often exhibit erosion and ulceration. A wide excision with a normal skin margin exceeding 5 mm is recommended. Lymph node dissection should be considered in T4 cases because of the high rate of lymph node metastasis associated with sebaceous carcinomas. Chemotherapy and radiation therapy may also be useful.⁷⁶

Trichilemmal carcinoma

The outer hair root sheath consists of cells with clear vacuolated cytoplasm due to the presence of abundant glycogen. Trichilemmal carcinomas are malignant tumors of these cells. They include malignant trichilemmoma, malignant pilomatricoma, and malignant proliferating trichilemmal cyst (Fig. 28.64). The latter is thought to be derived from proliferating trichilemmal cyst,³² while malignant pilomatricoma is believed to be derived from pilomatricoma. Clinically, these tumors present as pale tan or reddish papules, indurated plaques, or nodules. Wide excision should be performed as a radical therapy.

Sweat gland carcinoma

There are many types of eccrine and apocrine carcinomas. These malignant primary cutaneous tumors exhibit glandular and/or ductal features that are thought to reflect their origin

BOX 28.5 Histological classification of basal cell carcinoma (BCC)

1. Multifocal superficial BCC (superficial multicentric)
2. Nodular BCC (solid, adenoid cystic)
3. Infiltrating BCC
 - 3.1. Nonsclerosing
 - 3.2. Sclerosing (desmoplastic, morpheic)
4. Fibroepithelial BCC
5. BCC with adnexal differentiation
 - 5.1. BCC with follicular differentiation
 - 5.2. BCC with eccrine differentiation
6. Basosquamous carcinoma
7. Keratotic BCC
8. Pigmented BCC
9. BCC in basal cell nevus syndrome
10. Micronodular BCC

(Reproduced from LeBoit PE, Burg G, Weedon D, et al (eds). *World Health Organization Classification of Tumors. Pathology and Genetics of Skin Tumors*. Lyon: IARC Press; 2006:10–33.)

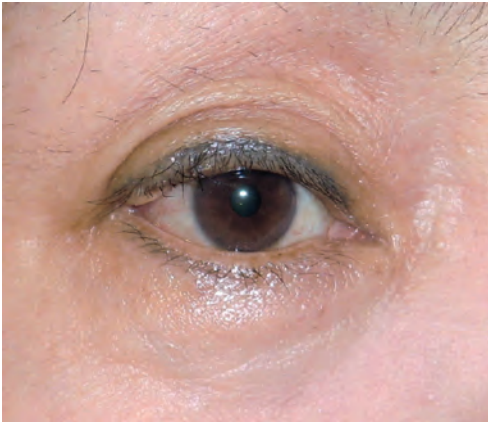


Fig. 28.63 Meibomian gland carcinoma on the upper eyelid.

as eccrine or apocrine ducts and/or glands. The diagnosis of sweat gland carcinoma requires that the tumor shows sweat gland features, as shown by extracellular ductal or intracytoplasmic lumen formation. This can be indicated by resistance to diastase, staining with periodic acid–Schiff stain, and immunohistochemical positivity for epithelial membrane antigen and carcinoembryonic antigen. The presence of S100 protein may also indicate sweat gland differentiation. Conventional surgical excision has been associated with high recurrence rates but Mohs micrographic surgery is helpful.⁷⁷ These carcinomas should be treated according to the guidelines for SCC.

Extramammary Paget's disease

Paget's disease is an adenocarcinoma that is limited to the epidermis. Since mammary Paget's disease is sometimes associated with invasive breast cancer, it can be considered as an intraepidermal proliferating breast carcinoma. In contrast, EMPD is only occasionally associated with an underlying invasive malignancy. It is usually found in the vulva, penis, and axilla. Since its invasive speed is relatively high, it can be difficult to detect early, especially if the lesion has been treated as eczema. Mohs micrographic surgery⁷⁸ or mapping biopsy is helpful for determining the normal skin margin for wide



Fig. 28.64 Malignant trichilemmal cyst.

excision (**Fig. 28.65**). Sentinel lymph node biopsy is also useful for deciding whether to remove the lymph nodes.

Merkel cell carcinoma

Merkel cell carcinoma is a rare and highly aggressive cancer where malignant cancer cells develop on or just beneath the skin and in hair follicles (**Fig. 28.66**). The majority of Merkel cell carcinomas appear to be caused by the newly discovered Merkel cell polyomavirus. It occurs most often on the face, head, and neck, and usually appears as firm and painless nodules or tumors. A normal skin margin of 1–2 cm is needed for wide excision. Moreover, since this tumor tends to metastasize to lymph nodes, lymph node dissection and adjuvant radiation therapy may have to be implemented.⁷⁹ Distant metastasis cases should also receive chemotherapy.⁷⁹

Malignant mesenchymal-origin tumors

Dermatofibrosarcoma protuberans (DFSP)

DFSP is also called giant cell fibroblastoma. Over 90% of DFSP tumors have the chromosomal translocation t(17;22) that fuses the collagen gene COL1A1 with the platelet-derived growth factor gene. Typically, DFSP occurs as multiple or solitary tumors that have a red color, hemispherical elevation, and papillary vessels on the surface (**Fig. 28.67**). They have a keloidal appearance, which has sometimes led to



Fig. 28.65 Mapping biopsy for extramammary Paget's disease.

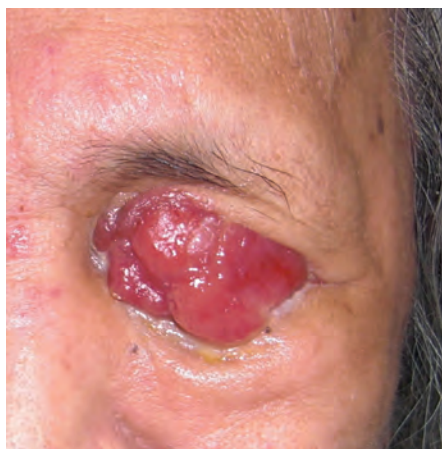


Fig. 28.66 Merkel cell carcinoma on the eyelid.



Fig. 28.67 Dermatofibrosarcoma protuberans on the abdomen.



Fig. 28.68 Malignant fibrous histiocytoma on the axilla.



Fig. 28.69 Liposarcoma on the thigh.

misdiagnosis and treatment with corticosteroids. They metastasize rarely, but distant metastasis to the lung can result from local recurrence. Radical resection should include a normal skin margin of 5 cm. Mohs micrographic surgery with continuous histological margin control is needed to reduce local recurrence rates.⁸⁰ Adjuvant chemotherapy and radiation therapy may be useful.

Pleomorphic undifferentiated sarcoma (PUS)

There are four types of malignant fibrous histiocytoma (which is more recently being classified as pleomorphic undifferentiated sarcoma⁸¹): (1) storiform-pleomorphic type; (2) myxoid type; (3) giant cell type; and (4) inflammatory type. Moreover, atypical fibroxanthoma is considered to be a superficial type (Fig. 28.68). Despite being called histiocytomas, these tumors are not believed to be derived from histiocytes. In fact, it is currently being argued on the basis of immunohistochemistry and electron microscopic observations⁸² that most of the storiform-pleomorphic type should be reclassified as liposarcomas, leiomyosarcomas, or rhabdomyosarcomas. Radical therapy involving wide excision is needed. Adjuvant chemotherapy and radiation therapy may also be useful.

Liposarcoma

Liposarcoma is derived from the fat cells in deep soft tissues such inside the thigh or the retroperitoneum (Fig. 28.69). They are generally large and bulky tumors with multiple smaller satellites located outside the main tumor. Diagnosis requires the detection of lipoblasts, which usually have an abundant, clear, multivacuolated cytoplasm and an acentric, darkly staining, vacuole-compressed nucleus. Dedifferentiated liposarcomas exhibit a dedifferentiated area in the tumor that sometimes results in osseous metaplasia.⁸³ Radical therapy involving wide excision is needed. Adjuvant chemotherapy and radiation therapy may be useful.

Leiomyosarcoma

This rare malignancy mainly occurs on the limbs of middle-aged and older patients (Fig. 28.70). It can be very unpredictable as it can remain dormant for long periods of time and recur after years. It is generally not very responsive to chemotherapy or radiation. However, neoadjuvant or adjuvant chemotherapies,⁸⁴ or radiation, are recommended.

Rhabdomyosarcoma

Rhabdomyosarcoma is thought to arise from skeletal muscle progenitors and occurs in many anatomic locations.



Fig. 28.70 Leiomyosarcoma on the face.

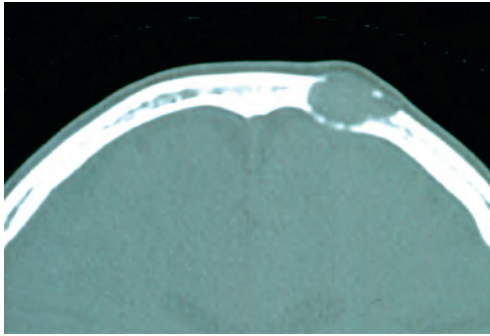


Fig. 28.71 Computed tomography of an osteosarcoma on the frontal bone.

Sometimes it is found attached to muscle tissue or wrapped around intestines. Mostly it occurs in areas that naturally lack skeletal muscle, such as the head, neck, and genitourinary tract. Its three most common forms are embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, and pleomorphic rhabdomyosarcoma. Embryonal rhabdomyosarcoma is more common in younger children, where the cancer cells resemble those of a typical 6–8-week embryo. Alveolar rhabdomyosarcoma occurs more commonly in older children and teenagers, and the cells resemble those of a typical 10–12-week embryo. Pleomorphic rhabdomyosarcoma is a rare sarcoma that occurs most often in older patients. Radical therapy involving wide excision is needed. There is also evidence that rhabdomyosarcomas are the target of host immune responses.⁸⁵

Osteosarcoma

This aggressive cancerous neoplasm arises from primitive transformed cells of mesenchymal origin that exhibit osteoblastic differentiation and produce malignant osteoids (Fig. 28.71). Complete radical surgical *en bloc* resection is the treatment of choice.⁸⁶ Some recent studies have suggested that osteoclast inhibitors such as alendronate and pamidronate may improve the quality of life by reducing osteolysis, which decreases the pain as well as the risk of pathological fractures.

Chondrosarcoma

At presentation, nearly all chondrosarcoma patients appear to be in good health as this form of cancer usually does not affect the whole body. Indeed, the patients are generally not aware of the growing tumor until there is a noticeable lump or pain. An earlier diagnosis is generally accidental, such as when a patient undergoes testing for another problem. Occasionally, the first symptom will be a broken bone at the cancerous site. Therefore, broken bones due to mild trauma warrant further investigation, even though there are many conditions that can lead to weak bones and this form of cancer is not a common cause of such breaks. Chemotherapy or traditional radiotherapy is not very effective for most chondrosarcomas, although proton beam radiation therapy is showing promise with regard to local tumor control.⁸⁷ Complete surgical ablation is the most effective treatment but can be difficult to achieve. Proton beam radiation can facilitate the surgical removal of chondrosarcomas in awkward locations.

Angiosarcoma

Angiosarcoma is the common name for malignant neoplasms of endothelial cells (Fig. 28.72) but it is replaced with the terms



Fig. 28.72 Angiosarcoma on the axilla.

lymphangiosarcoma and hemangiosarcoma when more clinical precision is required. Haemangiosarcomas and lymphangiosarcomas of the skin are not uncommon. Given the location of angiosarcomas, metastasis to distant sites occurs often. Surgery, radiation therapy, chemotherapy, and immunotherapy using interleukin-2⁸⁸ should be used, but the prognosis of these tumors is poor. However, the prognosis of neoplasia of superficial vessel tissues such as those in the skin is generally better because the risk of malignancy is lower; moreover, these tumors are generally more accessible to treatment.

Kaposi's sarcoma

Kaposi's sarcoma is caused by the Kaposi's sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8. It became widely known after its frequent appearance in acquired immune deficiency syndrome patients was noted in the 1980s. Although the viral cause of this cancer was discovered in 1994, this causal link remains poorly understood by the general populace, including by the groups that are at particular risk of contracting KSHV. Kaposi's sarcoma lesions present as red, purple, brown, or black nodules or blotches that are usually papular (i.e., palpable or raised). They are typically found on the skin but can often spread elsewhere, especially to the mouth, gastrointestinal tract, and respiratory tract. Their growth can range from very slow to explosively fast, and they are associated with significant mortality and morbidity. Radiation therapy, cryotherapy, and chemotherapy may be useful. Surgery is not the primary choice of treatment, although it may be useful as supportive therapy. Highly active antiretroviral therapy should be combined with these therapies.⁸⁹

Others

Other malignant mesenchymal-origin tumors include epithelioid sarcoma, synovial sarcoma, extraskelletal Ewing's sarcoma, histiocytic sarcoma, and Langerhans cell sarcoma. In general, treatment consists of induction chemotherapy, wide surgical excision, and then maintenance chemotherapy. Multi-agent chemotherapy has improved survival rates.



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Melanoma

Stephan Ariyan and Aaron Berger

SYNOPSIS

- The definitive diagnosis of melanoma is based on histologic analysis. Clinical features suggestive of malignancy include: asymmetry, border irregularity, color changes, diameter $> \frac{1}{4}$ inch, and evolving changes; the ABCDE criteria.
- The four major histopathologic subtypes of melanoma are: lentigo maligna, superficial spreading, nodular, and acral lentiginous. Desmoplastic melanoma is a less common subtype of melanoma that lacks pigment and may demonstrate perineural invasion.
- Initial work up of the pigmented lesion should include excisional biopsy with a 1–2-mm margin of normal-appearing skin. If functional or cosmetic concerns prohibit removal of the entire lesion, incisional or punch biopsy may be performed.
- Histologic evaluation of the primary lesion must include: Breslow depth in millimeters, presence/absence of ulceration, mitotic rate per mm^2 , peripheral and deep margin status, and Clark level (especially for lesions ≤ 1 mm in depth).
- Recommended excision margins are determined by Breslow depth. *In situ* melanoma requires a 0.5-cm margin of normal-appearing skin. For invasive melanoma, a 1-cm margin is recommended for lesions ≤ 1 mm in depth, a 1–2-cm margin is recommended for lesions 1.01–2.0 mm in depth (dependent upon functional/cosmetic concerns), and a margin of at least 2.0 cm is recommended for lesions > 2.0 mm in depth.
- Subungual melanoma of the hand should be resected at the distal interphalangeal joint to preserve function.
- Sentinel lymph node biopsy (SLNB) is offered to patients with melanomas > 1 mm in thickness, and patients with thin melanomas (≤ 1 mm thick) that demonstrate high-risk features, including ulceration and/or high mitotic rate. The likelihood of detecting metastatic deposits in an SLNB increases with the thickness of the primary lesion.
- For patients with stage I and II disease, chest X-ray and liver function tests compose the recommended workup. Patients with regional (stage III) or systemic metastases (stage IV) should undergo a comprehensive staging workup that may include CT scans with PET imaging.
- Serum LDH (lactate dehydrogenase) is used in the AJCC staging system as it portends a worse prognosis in patients with metastatic disease.

- Patients with high-risk primary tumors or metastatic disease should be considered for adjuvant treatment with interferon-alfa or enrollment in a clinical trial.

Introduction

Few diseases are as fascinating and as troublesome to physicians as malignant melanoma, and perhaps no other disease elicits as much fear in the patient as does this diagnosis. Although it accounts for only 4% of all malignant neoplasms, its very diagnosis suggests to some patients an aggressive, rapid progression to death. The name alone may leave some patients with a sense of hopelessness that is often unjustified. Despite some reported descriptions of rapid spread, the natural history of melanoma and its overall cure rate of 80% compare favorably with those of cancers of the breast, colon, rectum, and oropharynx and are far better than for cancer of the lung.

Epidemiologic studies demonstrate that the incidence of melanoma has been increasing faster than that of any other cancer in the United States.¹ It is estimated that there were 76100 new diagnoses of melanoma and 9710 deaths in the United States in 2014.² Melanoma incidence rates doubled from 1982 to 2011.³ An individual dying from melanoma loses an average of 20.4 years of potential life.⁴

Our understanding of melanoma continues to improve, and we can now differentiate low-risk from high-risk patients on the basis of multifactorial analyses from several series of large numbers of patients. However, despite our best attempts to understand the molecular basis of this disease, limited success has been demonstrated in terms of new medical treatments, and successful treatment of this disease relies heavily upon the surgeon.



Access the [Historical Perspective](#) section, [Table 29.1](#) and [Figs. 29.1 & 29.2](#) online at

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Historical perspective

Although Hippocrates is credited with the first reported observation of what appears to be a melanoma, Handley⁵ attributes the first clinical case of malignant melanoma reported in England to Dr. William Norris. In 1820, Norris felt compelled to report this case because of the rapid spread of the tumor, which led to his patient's death. He reported that at the autopsy, every organ except the spleen and the bladder was riddled with "black specks".⁶ The patient's father had died of similar disease, and the patient's brothers and his children had "many moles on various parts of their bodies".

Handley had never himself treated a patient with a melanoma, but he made considerable observations after performing an autopsy on a 34-year-old woman who had died of disseminated metastatic melanoma. He was interested in the mechanisms of spread of melanoma. Halsted had already described the spread of breast cancer along the lymphatics surrounding the primary tumor.^{7,8} In his two Hunterian lectures, Handley proposed that the primary spread of melanoma was through the lymphatics and not by blood vessels. In his first lecture, he described his autopsy findings; the 34-year-old woman previously had a primary melanoma excised from her right foot over the Achilles tendon. At autopsy, Handley observed a large collection of tumor growths in the right groin and virtually every part of the body except the entire left leg (Fig. 29.1). Arguing incorrectly that every organ would have been involved if tumor spread were hematogenous, he stated that sparing of the spleen, bladder, stomach, and left leg could be explained by "lymphatic permeation". Although Handley did not discount the concept of hematogenous spread, he believed that early dissemination was by lymphatics and that invasion of the blood stream occurred later "either by local infiltration of veins from concomitant permeated lymphatics, or by malignant cells carried into the blood along the thoracic duct from invaded lymphatic glands".⁵

In his second lecture, Handley proposed that lymphatics were amenable to surgical removal with the primary melanoma. He based his treatment recommendations on histologic examination not of the primary site but of the regional groin recurrence. Indeed, Handley had confessed that "no opportunity of investigating the spread of permeation round a primary focus of melanotic growth has fallen to me".⁹

Nevertheless, because the site of the groin recurrence had shown "permeation spreading centrifugally in the lymphatic plexus of the deep fascia and invading skin and muscle secondarily over a smaller area", he advocated a wide radical resection for a primary melanoma (Fig. 29.2): "A circular incision should be made through the skin round the tumour ... situated as a rule about an inch from the edge of the tumour, should be just deep enough to expose the subcutaneous fat...

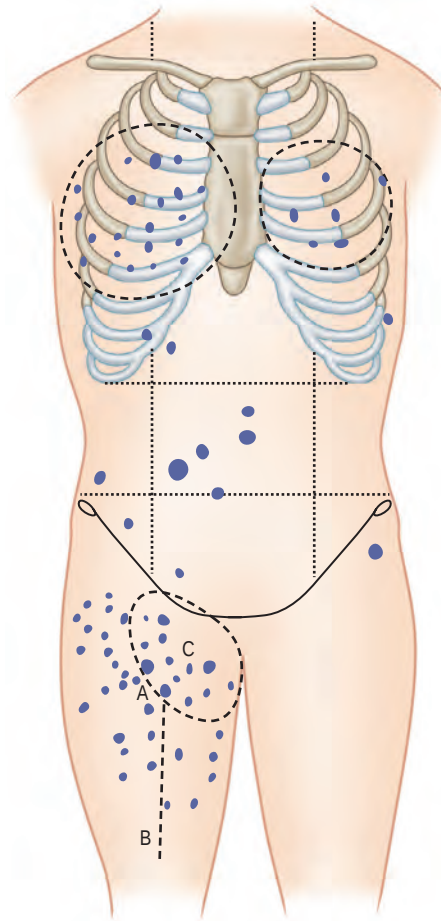


Fig. 29.1 Autopsy findings of patient with melanoma of right ankle spreading in a centripetal manner to right groin and remainder of body while sparing the left leg. (Redrawn from Handley WS. *The pathology of melanotic growths in relation to their operative treatment. Lecture I. Lancet. 1907;1:927.*)

The skin with a thin attached layer of subcutaneous fat is now to be separated from the deeper structures for about two inches in all directions round the skin incision.... Finally, the whole mass with the growth at its centre is removed by scooping out with a knife a circular area of the muscle immediately subjacent to the growth."⁹

This approach presented a minimal excision of 2.5 cm of skin and 5 cm of subcutaneous tissue surrounding the melanoma, down to and including the muscle fascia, as well as incorporating a portion of the underlying muscle. Therefore, it is this report by Handley, in which he recommended a 5-cm margin of skin and soft tissues around a melanoma, that appears to be the first such proposal for a wide margin of resection.

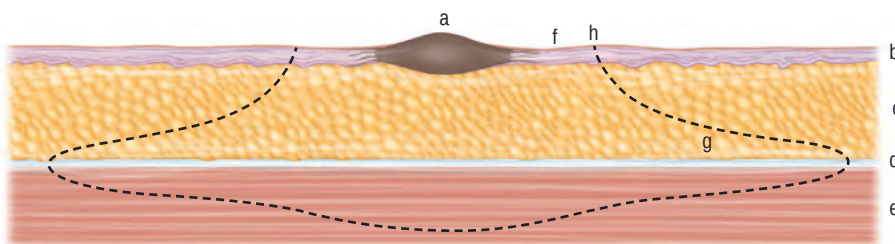


Fig. 29.2 Handley recommended removal of melanoma (a) together with 1 inch (f) of skin (b) and 2 inches (g) of underlying subcutaneous fat (c), muscle fascia (d), and muscle (e). h, skin incision. (Redrawn from Handley WS. *The pathology of melanotic growths in relation to their operative treatment. Lecture I. Lancet. 1907;1:927.*)

Handley believed that the regional lymph nodes also should be removed as part of the first operation. Furthermore, he advised that the excision of these glands be complete, “that is to say, a larger circular area of the surrounding deep fascia must be exposed, dissected up from its circumference towards the infected glands, and removed in one piece with them”. He then reported the treatment of a melanoma of the thigh by a senior colleague, A.P. Gould, by resection of the primary tumor and femoral nodes in this manner, but the patient had iliac node recurrence within 2 months.

In the year after Handley’s lecture, Pringle¹⁰ described three patients with melanoma whom he treated during the previous 10 years. However, Pringle further advocated removal of all subcutaneous tissue, including the lymphatics, between the primary site and the regional nodes together with the specimen. This was the first paper to describe the technique of an in-continuity dissection. He reported that one of his patients – a young woman who was alive 9 years after surgery at the time of the report – had moved to Canada, married, and had children. Pringle concluded in his report that “all that is removed should be in one continuous strip as far as possible”.

These early papers established the trends toward aggressive treatment of primary melanoma by wide excision of the tumor together with the underlying muscle and its fascia and by in-continuity lymph node dissection in an effort to achieve better cures. As Handley stated in his Hunterian lecture: “Nowadays the improved operation for breast cancer produces prolonged or permanent immunity in about 50 percent of cases. And upon the evidence I have laid before you I venture to predict that the application of more thorough and scientific methods to the surgery of cutaneous melanomata will produce a corresponding, though perhaps a smaller, improvement in the results of operation.”⁹

However, the methods of treating melanoma changed very little during the first half of the 20th century. The various reports of cure rates after aggressive surgical treatment of melanoma remained the same: a better prognosis if the patient did not have clinically palpable nodes (80% 5-year cure rate for stage I disease) than if the nodes were palpable (40% cure rate for stage II disease).¹¹

Subsequently, surgeons gained some information on prognostic factors of this tumor. Within each clinical stage, the prognosis is improved by the pathologic findings of no evidence of metastatic tumor cells on microscopic examination of the removed lymph nodes. However, the advantage of in-continuity removal of all tissues between the primary site

and the regional lymph nodes, as advocated by Pringle¹⁰ and as widely employed for decades, was challenged by Goldsmith *et al.*¹¹ who demonstrated no difference between this technique and that of discontinuous dissection of the primary tumor and the lymph nodes (Table 29.1). They, too, found no difference between immediate and delayed lymphadenectomy.

Finally, the issue regarding excision of underlying muscle and fascia was evaluated and resolved. Olsen¹² reviewed a series of 67 patients treated for melanoma in Denmark between 1949 and 1957. She found a 45% incidence of subsequent regional nodal metastases among the 31 patients who had the fascia removed during excision of the primary tumor and a 14% incidence of metastases among the 36 patients in whom this fascia was left intact. Because the patients who underwent a fasciectomy may have had more aggressive tumors, Olsen reviewed the next 51 patients treated from 1958 to 1961 who did not undergo excision of the fascia and observed only a 10% incidence of regional metastases. Kenady *et al.*¹³ reviewed their data of 202 patients treated at the M.D. Anderson Hospital, Houston, from 1961 to 1974 and found that local recurrence, regional nodal recurrence, distant metastases, and survival were not statistically different between the 107 patients who had the fascia excised and the 95 patients who did not. There appears to be no indication for removal of underlying muscle fascia unless the fascia becomes involved by contiguous tumor growth. In fact, the risk of lymphedema may be decreased by preserving the muscle fascia. In a series of 209 consecutive patients, 119 undergoing complete axillary lymphadenectomy, permanent upper extremity lymphedema occurred in 5% of the patients; and in 93 patients undergoing ilioinguinofemoral lymphadenectomy, permanent lower extremity edema occurred in 14% of the patients.¹⁴

Table 29.1 Outcome based on interval of timing of node dissection

Clinical stage	No. of patients	Nodal dissection	5-year cure rate	
			Simultaneous	Delayed
I	296	In continuity	63 (76%)	165 (78%)
		Discontinuous	15 (75%)	53 (75%)
II	435	In continuity	53 (42%)	167 (42%)
		Discontinuous	20 (35%)	195 (41%)

(Modified from Goldsmith HS, Shah JP, Kim DH. Prognostic significance of lymph node dissection in the treatment of malignant melanoma. *Cancer*. 1970;26:606.)

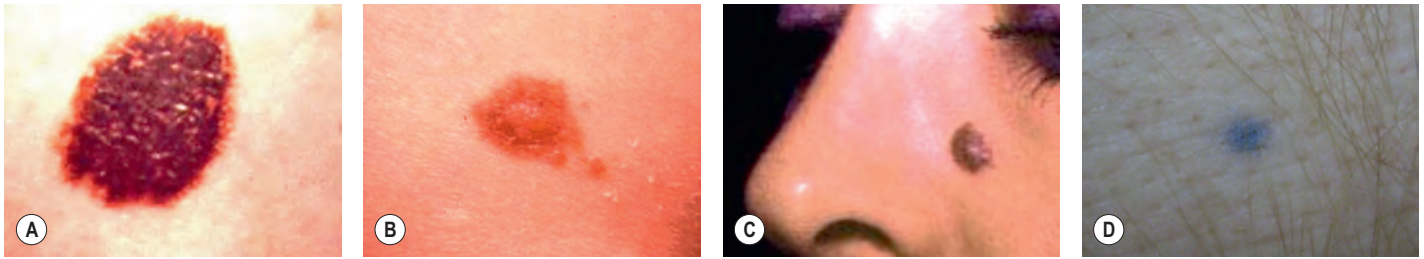


Fig. 29.3 (A) Junctional nevus is flat, smooth, and nonpalpable. (B) Compound nevus is developing into mature, thicker intradermal nevus in center within a flat junctional nevus in periphery. (C) Intradermal nevus is mature mole with elevation of the surface elements due to thickening of the layer of nevus cells. (D) Blue nevus presents with melanin deposits deep in the dermis reflecting the blue wavelength of light.

Clinical evaluation

Clinical diagnosis

The definitive diagnosis is not made until the specimen is examined histologically. Therefore, a review of the various pigmented lesions is essential for making a differential diagnosis.

All infants are born with nevi, but the lesions are usually not apparent at birth because they do not produce pigment. During the following few weeks or months, melanocytes produce pigment as a response to circulating hormones. As the nevi develop, they undergo maturation, which leads to the classification of the following various forms.

Junctional nevus

Junctional nevi are small flat lesions that first appear after birth and are smooth, nonpalpable, and light to dark brown or black (Fig. 29.3A). They are called junctional because the nevus cells are located at the interface of the epidermis and dermis. As the person develops and matures, the nevus cells grow and push into the dermis to develop into the common adult intradermal nevus.

Compound nevus

As the nevus matures, the central portion pushes into the dermis, causing this central portion to elevate and appear thicker (Fig. 29.3B). This nevus is called compound because the central portion is intradermal and thick, whereas the periphery is still junctional and flat. Compound nevi often are seen during adolescence, and the changes in such moles may cause concern to the patient, family, or primary care physician.

Intradermal nevus

The intradermal nevus is the common adult mole of the face or trunk that is elevated because of the maturation and proliferation of the nevus in the dermis, which now pushes up the overlying epidermis (Fig. 29.3C). It may be light or dark, usually is elevated, and may be sessile or pedunculated.

Blue nevus

Most nevi appear brown or black because the melanin is superficial and absorbs light. When the nevus contains melanin that is located more deeply, blue wavelengths of light

pass through the less pigmented epidermis and are reflected back to the eye as a blue nevus (Fig. 29.3D).

Congenital nevus

Congenital nevi differ from others in that they already produce pigment at birth (Fig. 29.4A). There is some controversy about



Fig. 29.4 (A) Congenital nevus is a large flat pigmented mole that has produced pigmentation *in utero* and is present as a pigmented lesion on the day of birth. It may be hairy (as in this case) or not. (B) Invasive (1.4 mm) melanoma developed within a congenital nevus on the trunk of a 57-year-old male.

whether congenital nevi are precursors of melanoma. Kaplan's review¹⁵ of the literature reported the transformation to melanoma to occur in 2% to 42% of congenital nevi (Fig. 29.4B). In a retrospective study of 234 melanomas by Rhodes and Melski,¹⁶ some of the histologic features of congenital nevi were found among 8% of the melanoma specimens. A systematic review of all studies evaluating the risk of melanoma in congenital nevi was performed by Krengel.¹⁷ A total of 6571 patients with congenital nevi were followed for at least 3.4 years, and 46 patients (0.7%; range 0.05% to 10.7%) developed 49 melanomas. Of note, primary melanomas arose inside the nevi in 67% of cases. Using age-adjusted data from the Surveillance, Epidemiology and End Results (SEER) database, they calculated that patients with congenital nevi carry an approximately 465-fold increased relative risk of developing melanoma during childhood and adolescence. Patients with large congenital nevi (Fig. 29.5), greater than 40 cm in diameter, were associated with the highest risk of developing melanoma, as well as dying from melanoma.^{17,18} However, the true incidence of the development of melanoma within congenital nevi is difficult to determine as the number of patients in the general population who have congenital nevi but never consult a physician, or eventually undergo excision, is unknown.

On the basis of available information about the potential for malignant transformation, it is a good policy to remove congenital nevi if it can be done without much difficulty or disfigurement (see Fig. 29.5). Malignant transformation does not usually occur before adolescence, thus, if the lesion is to be excised, it should be done before adolescence. Because it is difficult to excise nevi from the skin of children under local anesthesia and general anesthesia is often necessary for children younger than 12 years, the risk of complications from general anesthesia should be weighed against the risk of malignant transformation before adolescence. On the other hand, patients may request removal of the lesion to improve their appearance. Despite concerns for appearance, some lesions cannot be completely removed because in doing so we may cause a greater deformity. These lesions may require staged excisions.

Atypical (dysplastic) nevus

The atypical nevus is a clinical diagnosis of a nevus with melanocytes involving the epidermis and dermis that have features suggestive of malignancy. Clinically, it is large (>6 mm), with a macular surface, irregular margin, and

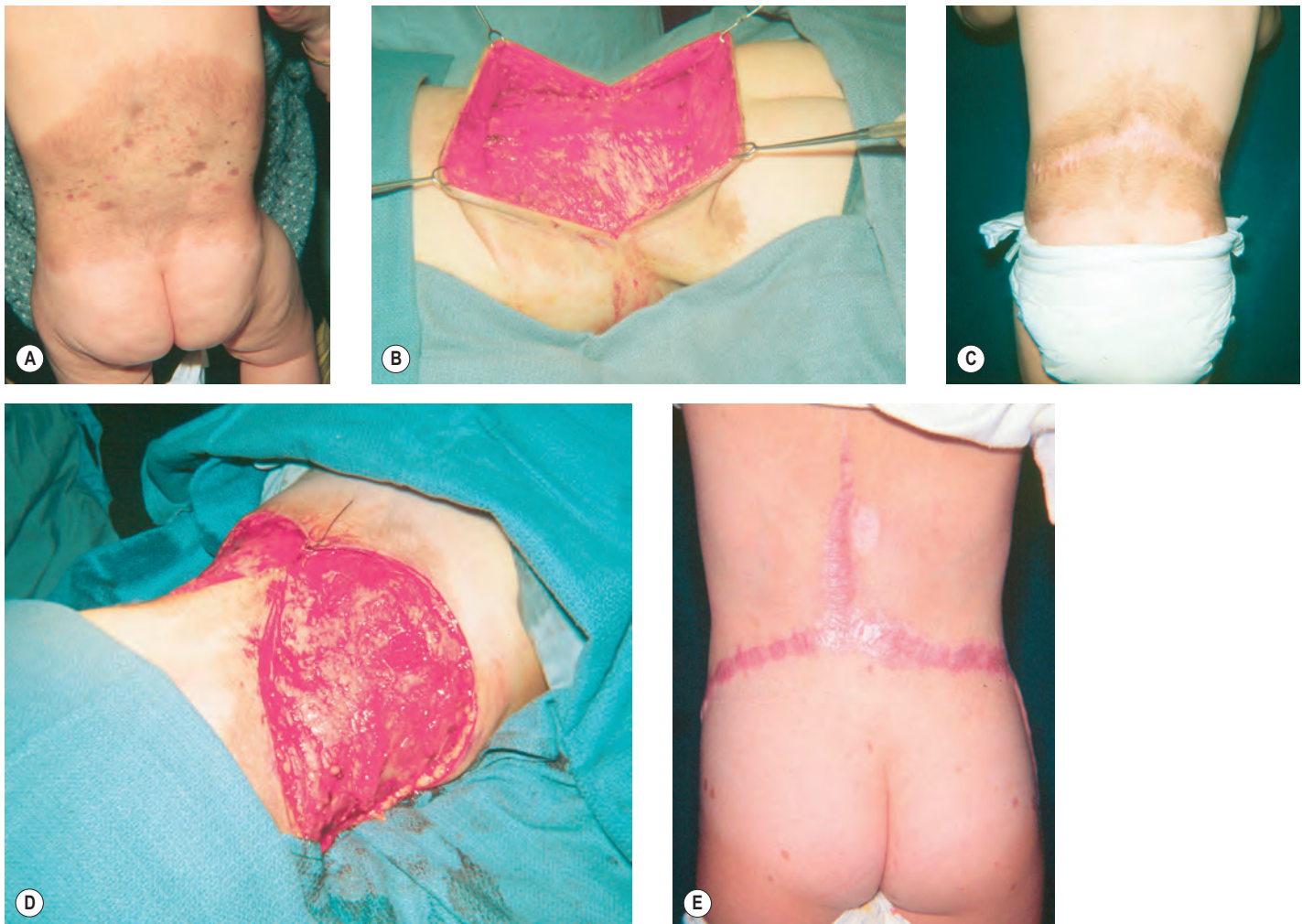


Fig. 29.5 Staged excision. A large truncal congenital nevus (A) was excised from the central portion of the lesion (B) to reduce the size of the lesion to half after one operation (C). A second procedure a year later (D) removed the remainder of the lesion (E).

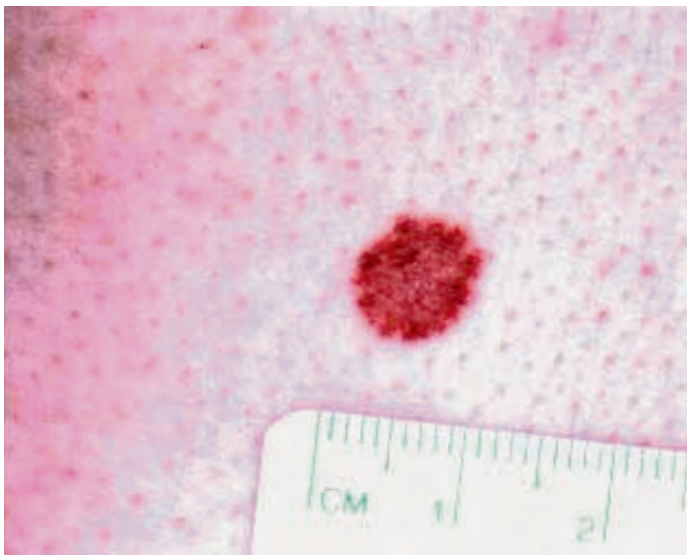


Fig. 29.6 Dysplastic nevus is a histologic confirmation of the clinical entity called atypical nevus. This is a large (>6 mm) flat mole of varying coloration.

variegated color. It may have a background of erythema (Fig. 29.6). These are benign lesions with histologic features that are abnormal. At various times, they have been called atypical nevi or dysplastic nevi. A National Institutes of Health Consensus Conference in 1992 recommended the descriptive term *atypical nevus* for the clinical diagnosis and the histologic term *dysplastic nevus* to describe the histologic degree of atypia and architectural disorder.¹⁹

To ensure accurate diagnosis, histologic examination of the lesion is required. Microscopically, the dysplastic nevus has melanocytic hyperplasia, with the melanocytes arranged as solitary units or small elongated nests oriented parallel to the long axes of the rete ridges. The melanocytes have nuclear atypia and abundant cytoplasm with a fine “dusty pattern” of melanin deposits.²⁰ Dysplastic nevi are often associated with atypical melanocytic hyperplasia, lymphocytic infiltration, and some evidence of regression. As such, patients with these lesions are believed to be at greater risk for transformation to melanomas.

Atypical (dysplastic) nevus syndrome

Studies at several institutions have found atypical nevi in association with melanoma that has no familial pattern. At the University of Pennsylvania, Elder *et al.*²¹ first described this as the dysplastic nevus syndrome in their 1980 report. In the same year, the Yale Melanoma Unit visited the Sydney Melanoma Unit in Australia and documented the presence of atypical nevi in 37% of 296 patients with melanoma who had no known family history.²² Similar atypical nevi were discovered in only 7% of a control population of male prison inmates without any history of melanoma.²² Clinically, these moles were large and resembled the dysplastic nevi of familial melanoma. Biopsies showed a 90% correlation between the histologic diagnosis of dysplastic nevi and the clinical appearance of these atypical moles. The tendency to develop atypical nevi is presumed to have a genetic basis, and the diagnosis of “atypical nevus syndrome” has been applied to patients with a range of phenotypic expressions,²³ including just the

presence of multiple atypical nevi and no personal or family history of melanoma, to the familial atypical multiple mole and melanoma syndrome.²⁴

B-K mole syndrome

Some prospective studies have shown that melanoma may be associated with a familial distribution in 10% to 11% of cases.²⁵ These familial melanomas tend to appear earlier and are distributed among dysplastic nevi over the body, with an excess over the trunk and a deficit over the upper extremities. Clark *et al.*²⁶ and Reimer *et al.*²⁷ suggested the role of atypical moles and dysplastic nevi in the development of hereditary melanoma when they described these moles in association with melanomas in seven families. They applied the initials of the first family, which were B.K., to name this clinical entity the B-K mole syndrome.

Differential diagnosis

The clinician is faced with the task of differentiating the malignant melanoma from a number of other lesions that may clinically resemble melanoma, such as seborrheic keratosis (Fig. 29.7A), pyogenic granuloma (Fig. 29.7B), and pigmented basal cell carcinoma (Fig. 29.7C). This differentiation may sometimes be difficult because of recent growth, bleeding into a lesion, or peripheral inflammation. In these instances, only microscopic examination of the tissue provides the proper diagnosis.

Extensive or radical surgical procedures should not be performed without the proper diagnosis of a melanoma because clinical impressions are not uniformly correct. Epstein *et al.*²⁸ reviewed 559 patients with black lesions that they believed might be melanomas. They found that their diagnosis of melanoma was correct only a third (38.7%) of the time. The most common diagnoses were benign nevi (35%), pigmented basal cell cancer (30%), and benign angiomas or vascular lesions (13%). Only 2% of the lesions were found to be melanoma. Dermoscopy, the use of a hand-held lens in combination with oil immersion, has been shown to improve diagnostic accuracy in skilled hands.^{29,30} However, it is used routinely by only 23% of dermatologists.³¹ In general, the diagnostic work-up of melanocytic lesions will precede the surgeon's involvement, unless the lesion is in a region of cosmetic concern.

Hutchinson freckle

A Hutchinson freckle is a flat, brown, macular lesion that may grow at various rates and achieve different shades of pigmentation (Fig. 29.8). This lesion occurs most commonly on the face, neck, and other sun-exposed surfaces of adults in middle age or later. On histologic examination, this lesion appears as an overgrowth of melanocytes at the epidermis–dermis junction. Although lentigo maligna is an *in situ* melanoma, invasive melanoma may develop within a Hutchinson freckle and is then called lentigo maligna melanoma.

Melanoma

Melanoma lesions may be flat or nodular, with significant darkening, erythema, or bleeding. On histologic examination, the earliest lesions demonstrate atypical melanocytes migrating above the dermis–epidermis junction and appearing



Fig. 29.7 Pigmented lesions that need to be differentiated from a melanoma. (A) Seborrheic keratosis of cheek is a velvety smooth keratosis that may turn dark brown to black with drying of the keratin layer. (B) Pyogenic granuloma with exophytic granulation tissue and darkening due to desiccation of the blood and coagulum. (C) Pigmented basal cell carcinoma with heaped up “pearly” margins. Pigment may represent hemosiderin or melanin granules from melanocytes that may be incorporated into the lesion.

within the upper portions of hair follicles and eccrine ducts. These changes are typical of melanoma *in situ*.³² Special staining with S100 and HMB45 may be necessary to confirm the diagnosis in cases with histologic features that may be equivocal. However, when even a single atypical melanocyte invades from the dermis–epidermis junction down into the dermis, the diagnosis is melanoma.³³

There are clinical features of pigmented lesions that are characteristic for melanoma. These criteria have been promoted by the American Cancer Society as the ABCD Guidelines (Fig. 29.9).

- A Asymmetry of the lesion as it grows from a round or oval lesion
- B Border irregularity, which is a result of irregular growth rates of different parts of the lesion
- C Color changes representing pigment granules deposited at varying depths in the dermis, depending on the rate of invasion
- D Diameter of the lesion becoming more than $\frac{1}{4}$ inch (>6 mm)

In addition to the above ABCD criteria, a review of the literature recommended the addition of E for “evolution”, in order to emphasize the significance of evolving pigmented lesions in the natural history of melanoma, especially given the existence of small-diameter (≤ 6 mm) melanomas.³⁴ In treating patients with suspicious pigmented lesions, physicians should be attentive to changes (evolving) of size, shape, symptoms (itching, tenderness), surface (especially bleeding), and shades of color. An investigation of the recognition process of melanoma by 135 dermatologists revealed that most dermatologists rely more on the lesion’s overall pattern, the “ugly duckling sign” (i.e., unique appearance relative to the patient’s other nevi), and recent change according to the patient, rather than the more well-known ABCD algorithm.³⁵ This observation lends support to the addition of an E category for evaluation of melanocytic lesions by the non-dermatologist.

Based on existing literature, most patients who present to their dermatologist are unaware of an existing melanoma. Most melanomas (56.3%) detected in the general dermatology practice are found by the dermatologist during routine physical examination, and are not part of the presenting

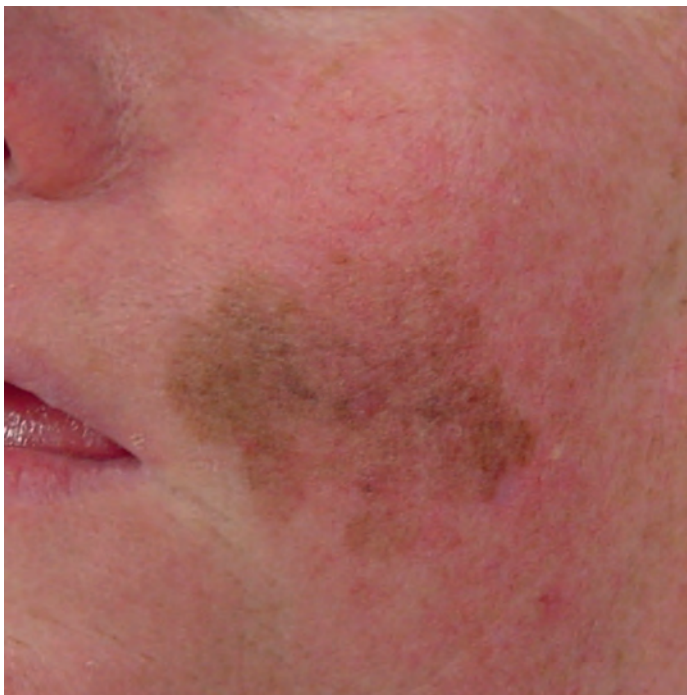


Fig. 29.8 Hutchinson freckle is a flat lesion with various shades of pigmentation.

complaint.³⁶ Numerous studies^{37–39} demonstrate that physicians are more likely to detect melanomas at a thinner stage than non-physicians. In these studies, there was a significant difference between the thickness of physician-detected melanomas (0.23–0.68 mm) and those detected by patients or their spouses (0.9–1.43 mm).

An occasional, and potentially reassuring, feature of melanoma is intralesional depigmentation (Fig. 29.10). This is a manifestation of immunologic regression of the tumor as a result of the destruction of the melanoma cells by the host's immune system. The histologic examination of only a section through the depigmented portion may be misread as an inflammatory reaction. However, deposits of residual melanin granules may exist in the depigmented portion (Fig. 29.10B), and histologic examination of sections through the adjacent pigmented portion may reveal the true diagnosis of the melanoma.

Nevertheless, depigmentation does not always indicate melanoma; a halo nevus (Fig. 29.11A) is a benign lesion with a peripheral ring of depigmentation.⁴⁰ Histologic examination of the halo portion shows lymphocytic infiltration without pigment granules (Fig. 29.11B). Further evaluation of the lesion and surrounding tissue shows no evidence of cells of malignant melanoma (Fig. 29.11C).

Multiple primary melanomas

Multiple primary melanomas have been reported to occur among 3% of melanoma patients.⁴¹ The risk for a second melanoma in a patient with one melanoma approaches 4% to 5%.⁴² However, with a positive family history of melanoma, the risk for multiple primary melanomas rises to 10% or more.⁴³ The highest risk of all appears to be in individuals who have a family history of melanoma in one or two first-degree relatives and who have clinical evidence of dysplastic nevi, suggesting

a probability approaching 100% in time.⁴⁴ Although multiple primary melanomas may be found among 10% of the patients, Ariyan *et al.*⁴⁵ reported that half of these subsequent melanomas are *in situ*, and the vast majority of the rest are less than 1.0 mm thick; thus, they did not seem to affect cure rates.

Classification/staging of disease

Melanoma is most commonly located in the skin, although it may also occur rarely in the mucosa of the oral cavity, nasopharynx, esophagus, vagina, and rectum. The staging system developed for melanoma applies to lesions arising in the skin, and thus, the discussion in this chapter is primarily limited to cutaneous melanoma.

The purpose of a classification system in malignant disease is to separate varying stages of severity to predict prognosis and to propose treatment options based on those predictions. Therefore, all classification systems have evolved from data collected over time. As such, each of these classifications needs to be re-evaluated periodically to refine the separation of stages on the basis of changes in outcome. Melanoma staging has evolved to include important data acquired from pathologic analysis of the initial biopsy (and potential biopsy of regional lymph nodes).

The most recent (2017), eighth edition of the American Joint Committee on Cancer (AJCC) staging system relies upon data related to the primary *tumor* (T), regional *lymph nodes* (N), and *metastases* (M). Also known as the TNM system, this staging system was developed based upon analysis of over 38 900 patients with cutaneous malignant melanoma⁴⁶ (Tables 29.2 & 29.3).

Histologic subtypes of melanoma

While morphology, or histologic subtype, does not necessarily correlate with clinical behavior, subclassification is important for pathologic recognition and diagnosis. Melanoma may be classified morphologically into four major growth patterns: lentigo maligna, superficial spreading, nodular, and acral lentiginous types (Fig. 29.12). Superficial spreading melanoma (Fig. 29.12B) represents 50% to 80% of all the types and is characterized by growth in the radial (horizontal) phase for a period of years before evolution into the vertical growth phase. Nodular melanoma (Fig. 29.12C), on the other hand, evolves into the vertical growth phase early in its development and represents 20% to 30% of the group but in some series may compose the majority of the lesions.⁴⁸ Lentigo maligna melanoma (Fig. 29.12A) is differentiated from superficial spreading melanoma and nodular melanoma by its location on sun-exposed surfaces of the body and within pre-existing lentigo maligna (Hutchinson freckle). This morphologic type of melanoma was believed to have a better prognosis than other types by virtue of a different biologic behavior, but it has been shown to have a prognosis identical with that for superficial spreading melanoma with comparable depths of invasion.⁴⁹ It has been shown that lentigo maligna melanoma merely grows in a horizontal fashion more than in a vertical fashion, resulting in thinner lesions than superficial spreading melanoma or nodular melanoma, which is the reason for its purported better prognosis.

Acral lentiginous melanoma appears on the palms of the hands, soles of the feet (Fig. 29.12D), subungual areas of the

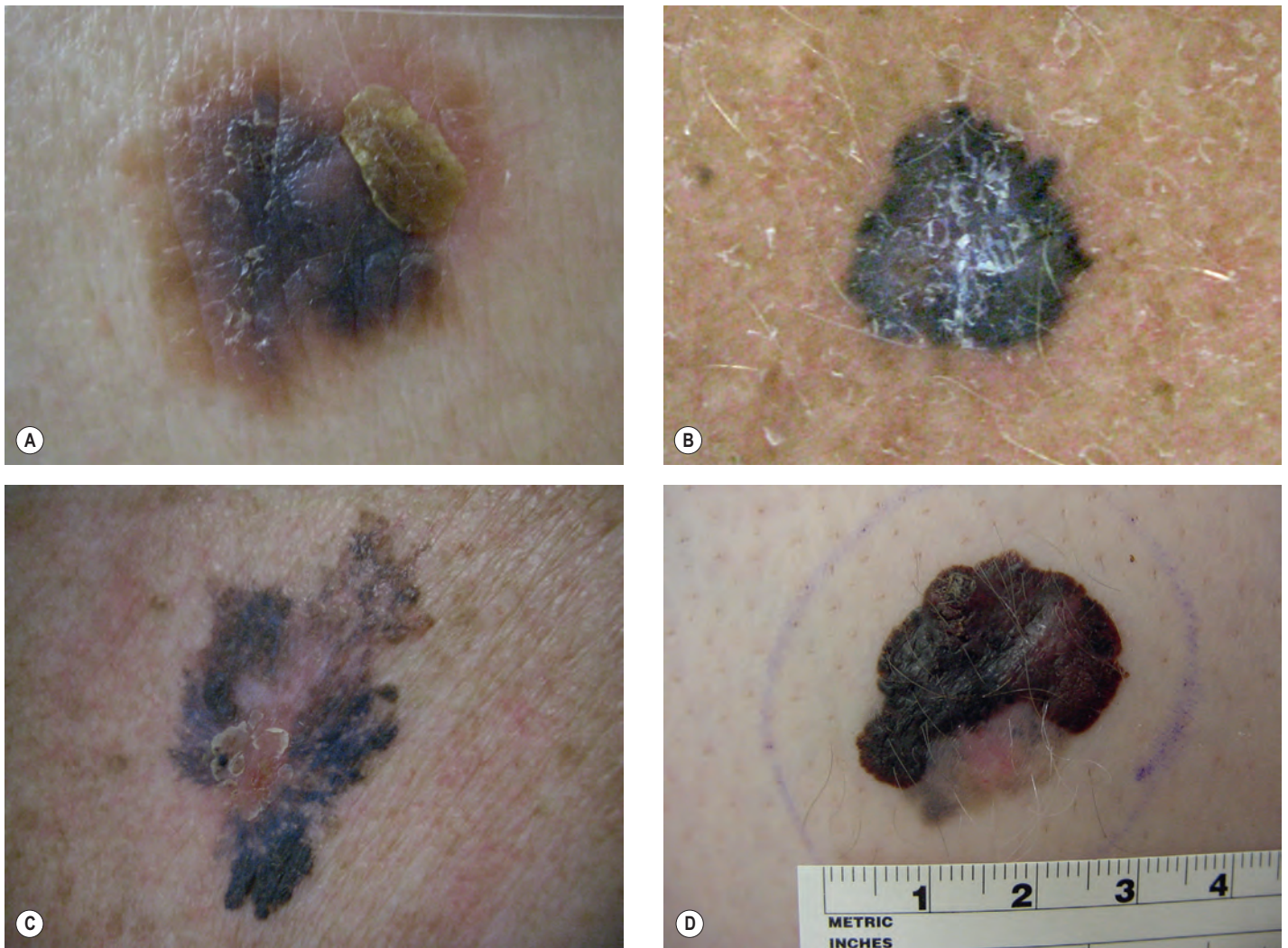


Fig. 29.9 Melanoma with characteristic changes. (A) Asymmetry of lesion shape. (B) Border irregularity. (C) Color variegation. (D) Diameter greater than 6 mm.

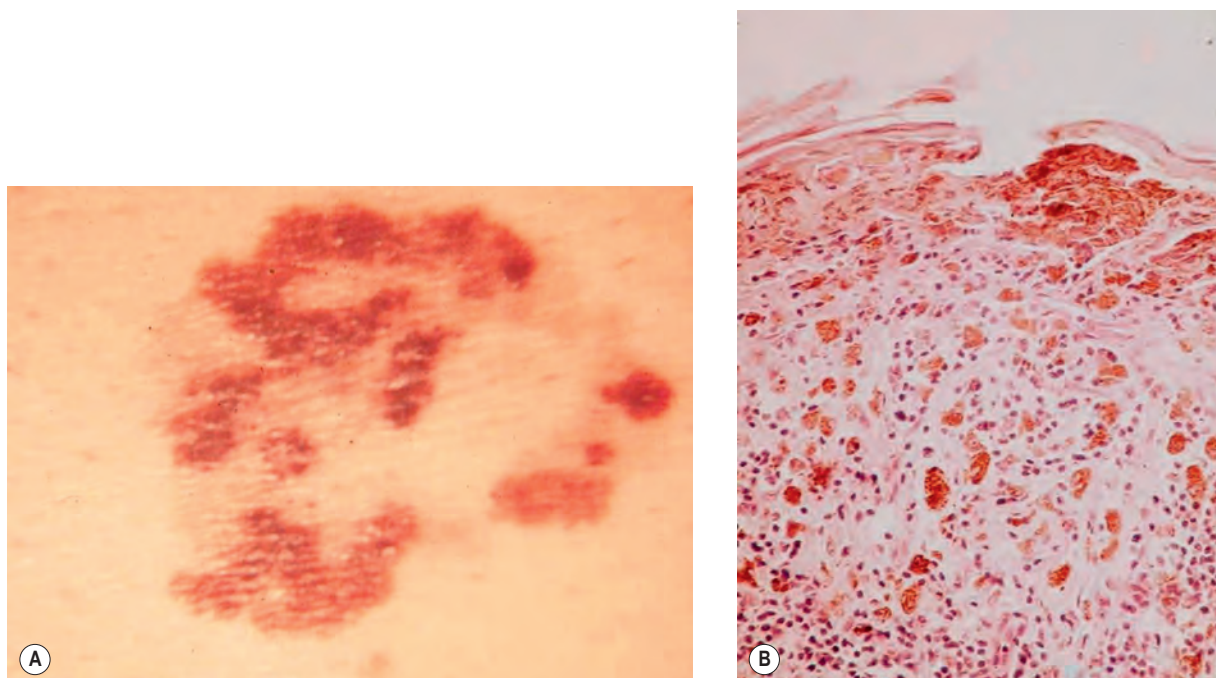


Fig. 29.10 (A) Melanoma with areas of depigmentation within the lesion. (B) Histologic examination of the specimen cut through the area of depigmentation shows significant lymphocytic infiltration with disrupted pigment granules leading to the colorless patches within.

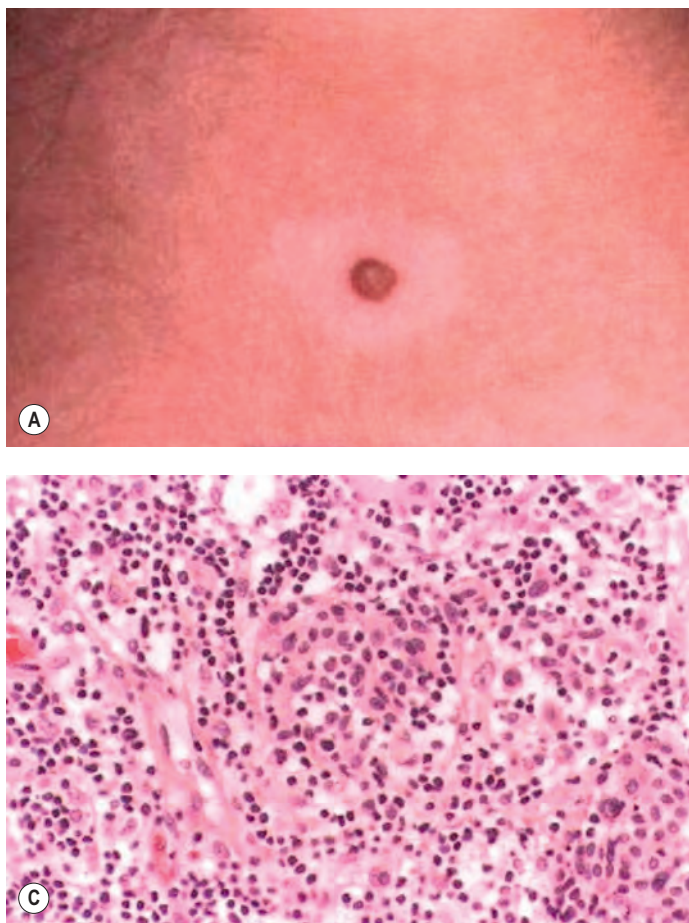


Fig. 29.11 (A) Halo nevus with a ring of depigmentation surrounding the lesion. (B) Histologic examination of the depigmented portion shows infiltration with lymphocytes, but there is no evidence of pigment granules or malignant cells (C).

fingers and toes (Fig. 29.12E), and web spaces.⁵⁰ The importance of subungual melanoma is that it is often erroneously believed to be a fungal infection, and appropriate treatment may be inadvertently delayed because of a delay in obtaining diagnostic biopsy. Presumably due to delayed diagnosis, this type of melanoma has the lowest 5-year survival rates of all histologic variants, generally found to be in the range of 10% to 20%.^{25,51}

While older studies suggested that prognosis may be associated with histologic subtype (e.g., patients with nodular melanomas were thought to have a worse prognosis than patients with superficial spreading melanomas),⁵² more recent multivariate analyses demonstrate that these prognostic differences are more likely due to other histologic features (i.e., tumor thickness and ulceration).⁵³

Another less common clinical variant of melanoma, desmoplastic melanoma, usually does not produce pigment, and grows on the external surfaces of the skin. It may have the appearance of a hypertrophic scar (Fig. 29.13A) at a location where the patient does not recall having had an injury to the skin. It must be differentiated clinically from a dermatofibroma and other benign or malignant tumors of the dermis. Histologic examination reveals a cicatricial growth of the lesion with spindle cell variants of malignant melanocytes (Fig. 29.13B,C).^{54–56} This histologic subtype must be differentiated from amelanotic melanoma (Fig. 29.14), which is simply a variant of nodular or superficial spreading melanoma that is not producing sufficient pigment granules to appear as a pigmented lesion. In one series of melanomas, the incidence

of amelanotic melanoma was found to be 1.8%.⁵⁷ Desmoplastic melanoma (DM) is subtyped to those that are pure DM (100% are spindle cells) and those that are mixed DM (not all are spindle cells), because of the lower risk of nodal metastases reported in the pure DM.⁵⁸

Histopathologic factors of prognostic significance

With respect to analysis of the primary lesion alone, the depth of invasion of melanoma into the dermis has been shown to be the most powerful determinant of outcome. In 1965, Mehnert and Heard⁵⁹ reported the earliest correlation of depth with prognosis. A few years later, Clark *et al.*⁶⁰ described the following system of levels for the classification of depth of invasion into the dermis (Fig. 29.15):

Level I: *In situ* melanoma; limited to the dermis–epidermis junction

Level II: Invading the papillary dermis but without expansion of this layer

Level III: Invading and expanding into the papillary dermis but not into the reticular dermis (to the interface of the papillary–reticular dermis)

Level IV: Invading the reticular dermis, but not into the subcutaneous fat

Level V: Invading the subcutaneous fat or the associated subreticular tissues

Table 29.2 Cutaneous melanoma TNM staging (AJCC 8th Edition)

T classification	Thickness	Ulceration status
Tis	not applicable	not applicable
T1	≤1.0 mm	a: <0.8 mm w/o ulceration b: <0.8 mm with ulceration 0.8–1.0 mm with or w/o ulceration
T2	1.01–2.0 mm	a: w/o ulceration b: with ulceration
T3	2.01–4.0 mm	a: w/o ulceration b: with ulceration
T4	>4.0 mm	a: w/o ulceration b: with ulceration
N classification	No. of metastatic nodes	Nodal metastatic mass
N1	1 node	a: clinically occult micrometastasis* b: clinically detected macrometastasis** c: in transit met(s)/satellite(s) <i>without</i> metastatic nodes
N2	2–3 nodes	a: clinically occult micrometastasis* b: clinically detected macrometastasis** c: in-transit met(s)/satellite(s) <i>with</i> 1 metastatic node
N3	4 or more metastatic nodes, or matted nodes, or in-transit met(s)/satellite(s) <i>with</i> metastatic node(s)	a: clinically occult micrometastases* b: 1 clinically detected micrometastasis** c: 2 or more clinically detected micrometastases
M classification	Site	Serum LDH
M1a	Distant skin, subcutaneous or nodal metastases	(0): normal (1): elevated
M1b	Lung metastases	(0): normal (1): elevated
M1c	Other visceral (non CNS) metastases	(0): normal (1): elevated
M1d	Distant CNS metastasis	(0): normal (1): elevated

*Micrometastases are clinically occult nodes diagnosed after sentinel node biopsy.
 **Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.
 (Source: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the Skin. AJCC Cancer Staging Manual. 8th Edition. Springer; 2017, pp. 563–585.)

Table 29.3 Melanoma stage/prognostic groups

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b T2a	N0 N0	M0 M0
Stage IIA	T2b T3a	N0 N0	M0 M0
Stage IIB	T3b T4a	N0 N0	M0 M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1ab-2a T1ab-2a	N1a N2a	M0 M0
Stage IIIB	T1ab-2a T2b-3a	N1b/c N1a-2b	M0 M0
Stage IIIC	T1a-3a T1a-3a T3b/T4a T4b	N2c N3a-c N1 or + N1a-2c	M0 M0 M0 M0
Stage IIID	T4b	N3a-c	M0
Stage IV	Any T	Any N	M1

(Source: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the Skin. AJCC Cancer Staging Manual. 8th Edition. Springer; 2017, pp. 563–585.)

The difficulty with this classification system is the qualitative and somewhat subjective nature of determining the depth of invasion. Various pathologists examining a histologic slide of mid-dermal invasion often disagree on the Clark level of invasion; some may call it a level III, while others call it a deep level II, and still others call it an early level IV invasion. As a result of this difficulty, Breslow⁶¹ reported a method of quantitative measurement that employs a simple and readily reproducible system of microstaging. According to Breslow, the melanoma's depth of invasion is measured in tenths of millimeters as a thickness from the surface of the tumor in the epidermis to the deepest tumor cell identified by means of an ocular micrometer on the microscope. In a number of studies using multivariate analyses,^{46,48} Breslow's method has been shown to be the most powerful prognostic indicator for survival in early stage melanoma (i.e., disease limited to primary tumor). Additional factors shown, in appropriate multivariate analyses of several thousand patients, to be associated with recurrence and survival include: ulceration in the lesion, the mitotic rate within the lesion, the patient's age and sex, the site of the primary lesion, and the morphologic type of melanoma.^{46,62}

T category of TNM staging system

The histopathologic factors incorporated into the T category of the 2017 TNM staging system are the thickness of the primary tumor, i.e., the Breslow depth,⁶¹ and the presence or absence of ulceration of the overlying epithelium.⁴⁶

The thickness of the primary tumor (T) defines four categories (see Table 29.2):

T1: ≤1.0 mm

T2: 1.01–2.0 mm

T3: 2.01–4.0 mm

T4: >4.0 mm



Fig. 29.12 Various morphologic types of melanoma. (A) Lentigo maligna melanoma – thin, flat lesion within patchy discoloration of Hutchinson freckle. (B) Superficial spreading melanoma – flat lesion with cells proliferating in the horizontal plane. (C) Nodular melanoma – thicker lesion growing in a vertical plane. (D,E) Acral lentiginous melanoma of the foot and nail bed.

Increasing tumor thickness is closely correlated with poorer prognosis. The 10-year survival decreases progressively, from 96% for patients with primary lesions <0.5 mm thick to 54% for patients with lesions 4.01 to 6.0 mm thick.⁴⁶

The T categories are further subdivided into “a” or “b” based upon the presence or absence of ulceration (see [Table 29.2](#)). Ulceration is defined as the absence of an intact

epithelium over the melanoma. Outcomes in patients with ulcerated primary tumors are worse than in patients with primary melanomas of the same thickness but without ulceration. The mitotic rate was incorporated into the previous 2010 TNM staging system based upon the observation that it was the second most important prognostic factor in over 11000 patients with localized melanoma analyzed in the

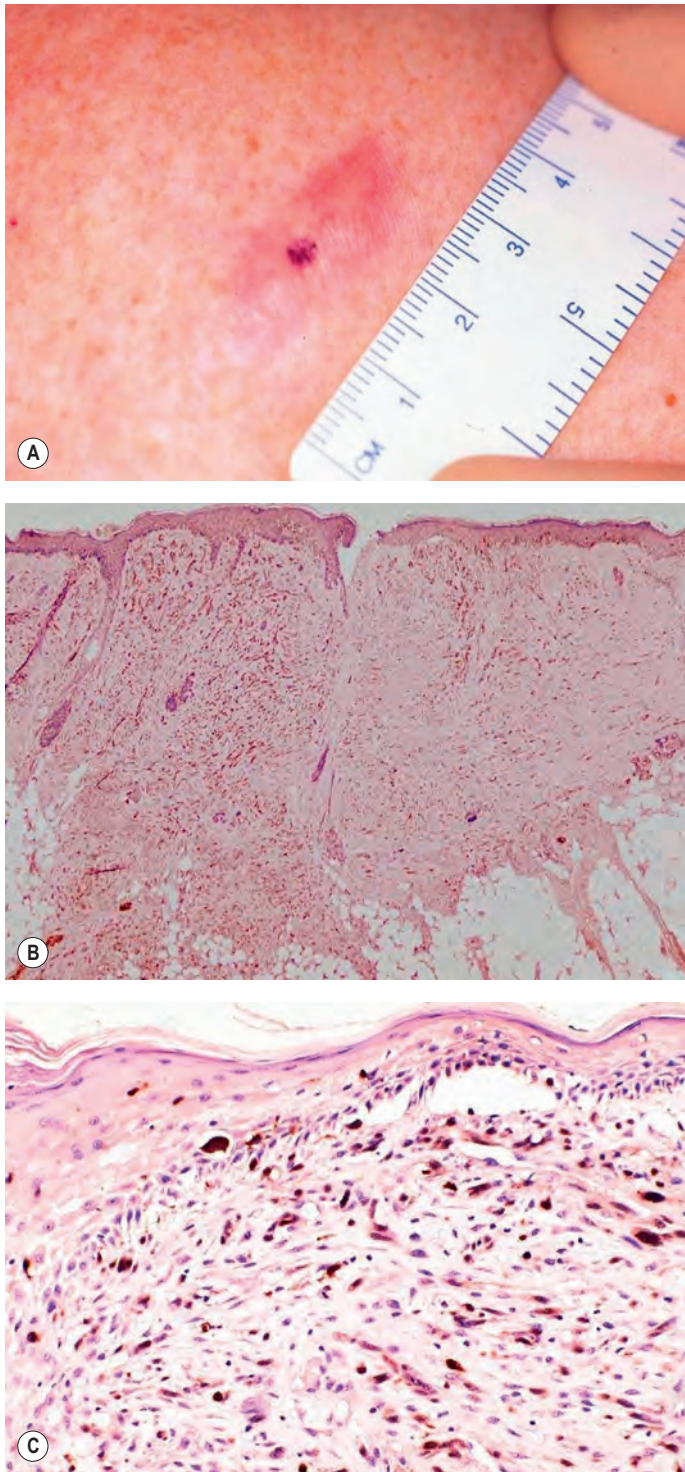


Fig. 29.13 (A) Desmoplastic melanoma is often nonpigmented and has the appearance of hypertrophic scar. (B) Low-power magnification of the desmoplastic melanoma shows the proliferation of the tumor in a cicatricial fashion. (C) High-power magnification of the lesion shows the spindle cell variant of the malignant melanocytes with the production of some pigment granules.

AJCC Melanoma Staging Database. In that series, there was a highly significant correlation between increasing mitotic rate and declining survival rates ($p < 0.0001$). For instance, for melanomas less than 1.0 mm thick, the 10-year survival rate was 93% for those with <1 mitosis/mm² and 48% for those with >20 mitoses/mm².^{46,47} The previously recommended approach to determining the mitotic rate was to identify the area of dermis containing the most mitoses (the “hot spot”), and average the number of mitoses within a 1-mm² area of the hot spot.⁴⁷ The substaging according to mitotic rates applied only to T1 lesions.

With respect to prognostic classification (see Table 29.3), Stage I melanoma defines patients with low-risk melanomas (T1a–T2a) without evidence of regional or distant metastases. Further subdivision (Stages IA and IB) is based upon characteristics of the primary tumor. Stage II melanoma includes primary tumors at a higher risk of recurrence or metastasis (T2b–T4b) without evidence of surgical or distant metastases. Similarly, stage II subdivision (IIA, IIB, IIC) is based upon characteristics of the primary tumor.⁴⁶ Details of more advanced stages of melanoma will be covered in the next section.

In-transit and regional lymph node disease

Local metastatic spread of cutaneous melanoma is known to occur through lymphatic channels in the majority – approximately 90% – of cases.⁶³ Direct hematogenous dissemination of melanoma, more difficult to assess and treat, is another less common route of metastasis. There are a number of clinical and pathologic characteristics of regional spread of metastatic melanoma that have become incorporated into the prognostic staging system for primary melanoma, namely satellite/in-transit metastases and sentinel lymph node status.⁶⁴

Intralymphatic spread of melanoma in the skin can present/manifest as satellite lesions, also known as *microscopic satellitosis*, or *in-transit metastases*, which are skin or subcutaneous metastases more than 2 cm from the primary lesion.⁵³ Microscopic satellitosis is seen in up to one-third of primary melanoma lesions greater than 3 mm thick, compared to less than

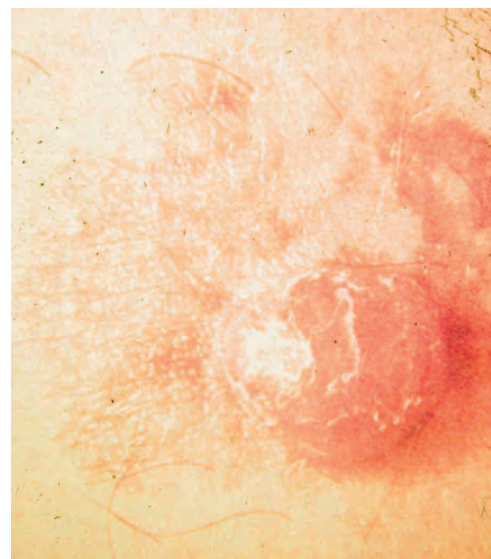


Fig. 29.14 The lack of pigment production in this amelanotic melanoma is deceptive in a lesion that is otherwise suggestive of malignancy.

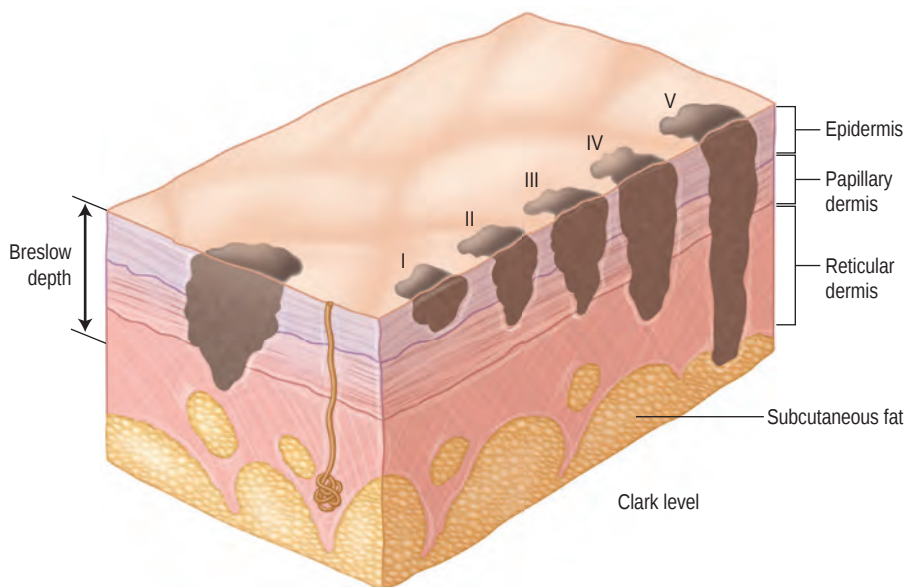


Fig. 29.15 The Clark classification of melanoma is dependent on the qualitative determination of the extent of invasion into the various areas of the dermis or subcutaneous fat. The Breslow classification is determined by the micrometer reading of the depth of invasion into the dermis, measured in tenths of millimeters.

5% of thinner lesions.⁶⁴ The presence of microscopic satellitosis and in-transit metastases has been shown to carry a poorer prognosis, similar to the presence of regional lymph node metastases.⁴⁶ Thus, in the current AJCC system, patients with microscopic satellitosis or in-transit metastases are upstaged to the level of a patient with established lymph node metastases (see [Tables 29.2](#) and [29.3](#)).

Spread of melanoma to the regional lymph nodes portends a poorer prognosis. As melanoma is known to mostly metastasize through lymphatic channels (and the first sites of metastasis are typically regional lymph node basins), evaluation of the regional lymph node basins has become critical in the staging of melanoma. Unfortunately, clinical evaluation of the regional lymph nodes is often inaccurate; as many as 20% of clinically node-negative patients have metastatic involvement on pathologic evaluation, and up to 20% of those with clinically positive nodes are pathologically negative.⁶⁵

Mostly of historical significance, elective lymph node dissection (ELND) has largely been supplanted by SLNB. However, brief mention is warranted. In the setting of clinically node-negative disease, ELND involves removal of all lymph nodes in a suspected draining basin. The rationale is that removal of subclinical regional disease may provide a survival benefit over a therapeutic node resection performed after regional disease becomes clinically evident. Performance of this procedure is now controversial, in the era of lymphoscintigraphy and sentinel lymph node biopsy, especially as most melanomas are being diagnosed early (thinner and less invasive), and the morbidity associated with a completion lymphadenectomy can be quite significant. Additionally, while a few retrospective analyses suggested ELND might improve survival by 25–40 percent,⁶⁶ most prospective randomized trials have not demonstrated a survival benefit from ELND.⁶⁷

Lymphoscintigraphy (lymphatic mapping) and sentinel lymph node biopsy

In the skin, as in all parts of the body, arterial blood pressure diffuses serum and nutrient material out of the vessels into

the interstitial tissue to nourish the cells. The breakdown products of metabolism are then picked up by the veins and taken back into the systemic system. Because the pressure in the arteries is greater than in the veins, more of this vascular fluid is diffused into the tissue than is taken away by the vein. To avoid the consequences of edema, lymphatic vessels (the micro sump pumps of the system) draw away this excess fluid and take it to the regional lymph nodes to filter the product before returning it to the systemic vascular system. This filtering function of the lymph nodes allows detection and attack of foreign bacteria, antigens, and cancer cells. It was this principle that permitted Sappey⁶⁸ to show the lymphatic patterns of the human body in 1874 by injecting mercury into the skin. Sappey's lines are a helpful guide to determine the likely directions of lymphatic spread. Subsequent experience has shown that lesions located more than 2 cm above or below a "belt line" drawn through the umbilicus usually drain to the axillary or groin nodes, respectively. Lesions more than 2 cm on either side of the midline drain to the lymph nodes on that respective side. Lesions within 4 cm of the vertical and horizontal bands may go to any one of the pairs of options ([Fig. 29.16](#)).

As a result of potentially unclear lymphatic drainage patterns, Sherman and Ter-Pogossian⁶⁹ introduced lymphoscintigraphy in 1953. They injected radiocolloid gold (¹⁹⁸Au) intradermally and used a gamma counter to detect the concentrated colloidal isotope in the filtering lymph nodes. This technique has since been modified with various other isotopes and colloids of various particle sizes for specific diagnostic purposes. The intent of each of these modifications is to identify the lymphatic vascular pattern in the tissue being evaluated.

The technique of lymphatic mapping is helpful for predicting the pattern of spread for cutaneous melanoma metastases to regional draining lymph node basins, and it may be helpful in actually detecting metastases in melanoma of the extremities.⁷⁰ In particular, the test may be useful in patients with T2 or thicker lesions of the lower extremity for evaluation of the iliac and pelvic lymph nodes to determine the extent of

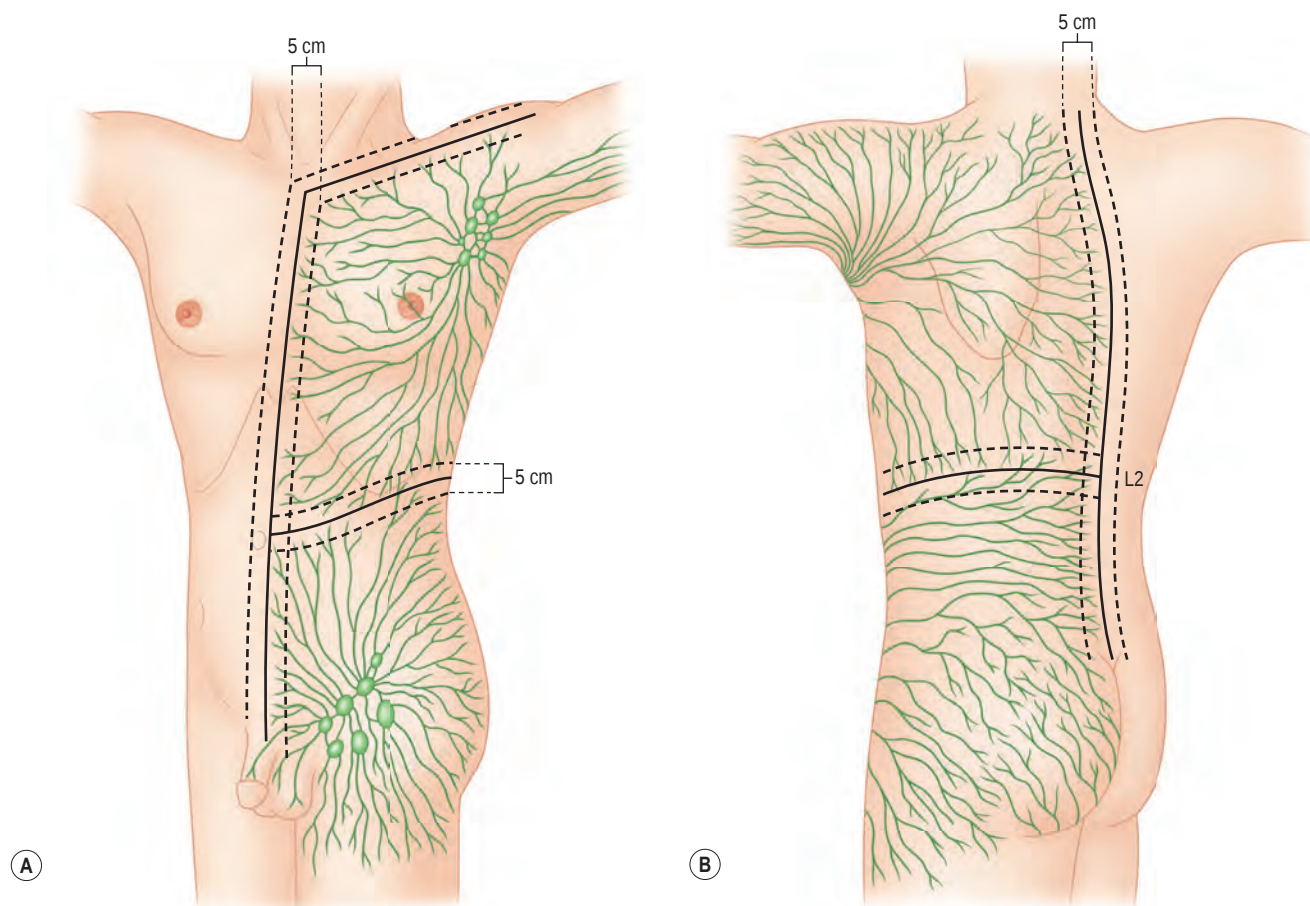


Fig. 29.16 (A,B) Lymphatic drainage as predicted by Sappey's lines. (Redrawn from Sugarbaker EV, McBride CM. *Melanoma of the trunk: the results of surgical excision and anatomic guidelines for predicting nodal metastasis*. *Surgery*. 1976;80:22.)

lymphadenectomy that may be indicated. The iliac nodes should certainly be removed if they appear to be involved, but a pelvic lymphadenectomy is not indicated if the para-aortic lymph nodes are involved because cure is unlikely in these cases.

The sites of lymphatic spread from melanoma at other locations, including the trunk and head and neck regions, may be also evaluated by radionuclide lymphoscintigraphy.⁷¹ Several radiocolloids have been employed for lymphoscintigraphy, including gold, sulfur, and antimony. Antimony sulfide colloid and technetium sulfur colloid have been found to be safe, and both give reliable information for determining appropriate lymph nodes for elective dissection among patients with truncal or head and neck melanomas (Fig. 29.17).

A lymphoscintigram can demonstrate predicted as well as unexpected patterns of lymph node drainage from lesions at primary sites. The test has been demonstrated as a reliable predictor of the sites of nodal involvement. In a prospective study of 51 consecutive patients with primary melanomas greater than 1 mm thick and observed for a mean of 45 months, 23% of the 35 patients who chose to undergo elective lymphadenectomy were found to have micrometastases to these lymph nodes; all were in the node groups detected by the lymphoscintigram.⁷² During the several years of their follow-up, 5 of the 16 patients (31%) who chose to be observed eventually developed clinical evidence of nodal metastases;

in each case, the nodes that were involved with tumor were at the very sites of drainage predicted by the lymphoscintigrams that were performed at the time of initial diagnosis (Table 29.4). During the 7-year interval of follow-up, no patient in either group developed metastases to any nodes not predicted by lymphoscintigraphy.

Sentinel lymph node biopsy

As stated previously, the availability of lymphatic mapping with SLNB has obviated a possible role for ELND in the treatment of cutaneous melanoma. The concept of the sentinel lymph node is based on the principle that all lymphatic fluid from specific tissues is filtered by lymph nodes, and as such the first (or sentinel) lymph node filtering a specific site can be removed and evaluated for metastasis of malignant cells. The validity of this entire principle is predicated on the tenets that: finite regions drain to a specific node; the sentinel node can be found; a negative biopsy finding means no other metastases exist; and a negative sentinel node is truly negative.

Morton⁶³ introduced the technique of detecting the sentinel lymph node with the intraoperative injection of vital blue dyes in the dermis surrounding the site of the primary melanoma. He identified the sentinel lymph node in more than 80% of the patients and reported that the false-negative

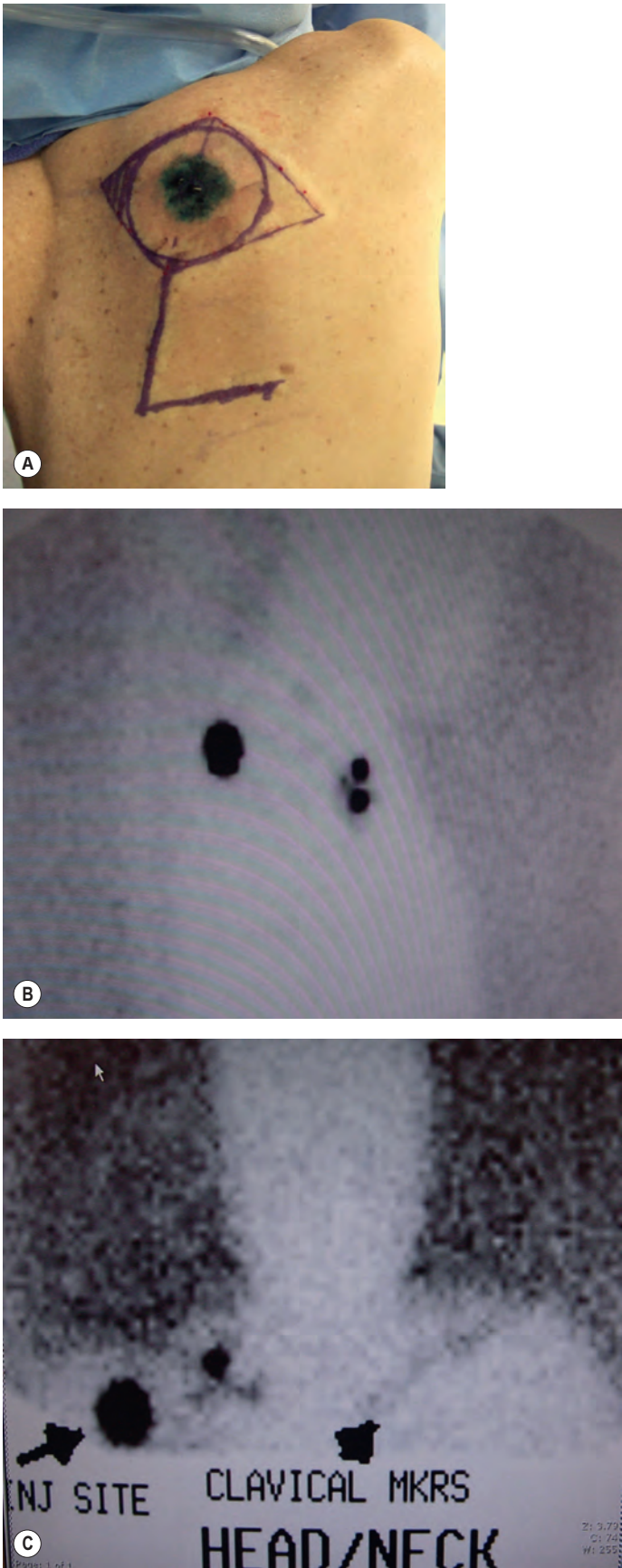


Fig. 29.17 Lymphoscintigram of a right scapular melanoma (A) demonstrates drainage to the right axillary lymph nodes (B), as well as the right lower cervical nodes (C).

Table 29.4 Reliability of lymphoscintigrams		
	ELND	Observe
Number of patients*	35 (70%)	16 (30%)
Lymph node metastases	8 (23%)	—
Subsequent lymph node metastases	—	5 (31%)
*51 patients with melanoma greater than 1 mm thick; 7-year follow-up (mean of 45 months). ELND, elective lymph node dissection. (Data from Stephens PJ, Ariyan S, Ocampo RJ, et al. The predictive value of lymphoscintigraphy for nodal metastases of cutaneous melanoma. <i>Conn Med.</i> 1999;63:387.)		

Table 29.5 Risk of detecting a positive sentinel lymph node	
Breslow depth	Risk of + SLN
<1.0 mm	4–7%
1.01–2.0 mm	12–20%
2.01–4.0 mm	28–33%
>4.0 mm	40–44%
(Data from Rousseau DL Jr, Ross MI, Johnson MM, et al. Revised American Joint Committee on Cancer staging criteria accurately predict sentinel lymph node positivity in clinically node-negative melanoma patients. <i>Ann Surg Oncol.</i> 2003;10:569–574 and Morton DL, Hoon DS, Cochran AJ, et al. Lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: therapeutic utility and implications of nodal microanatomy and molecular staging for improving the accuracy of detection of nodal micrometastases. <i>Ann Surg.</i> 2003;238:538–549.)	

rates had been about 5%. Subsequent investigators^{73–75} reported the use of preoperative lymphatic mapping and the intraoperative use of radiocolloids together with vital blue dyes with increased identification and successful removal of the sentinel lymph node to the range of 98% to 99% of patients with melanoma (Fig. 29.18). Based on studies of melanoma patients who underwent SLNB and subsequent completion lymphadenectomy of the respective lymph node basin, it can be assumed that if the sentinel lymph nodes are not involved, the entire basin should be free of tumor, in 96% of cases.^{63,73,76}

N category of TNM system

Sentinel lymph node biopsy has largely become the standard of care in the initial evaluation of cutaneous melanoma, particularly for patients with melanoma thicker than 1 mm in depth. The likelihood of finding nodal metastases in patients with tumors less than 1 mm in thickness is quite low (less than 10%).^{77–79} However, the presence of certain high-risk features, including ulceration and/or a high mitotic rate, may justify SLNB in thin melanomas.^{80–83} The likelihood of detecting metastatic deposits in an SLNB increases with the thickness of the primary lesion; for lesions <1.0 mm, 1.01 mm to 2.0 mm, 2.01 mm to 4.0 mm, and >4 mm, the risk is approximately 4–7%, 12–20%, 28–33%, and 40–44%, respectively (Table 29.5).^{84,85} The test is particularly useful for patients with intermediate thickness melanomas, 1–4 mm. However, it should still be considered in the treatment algorithm of patients with

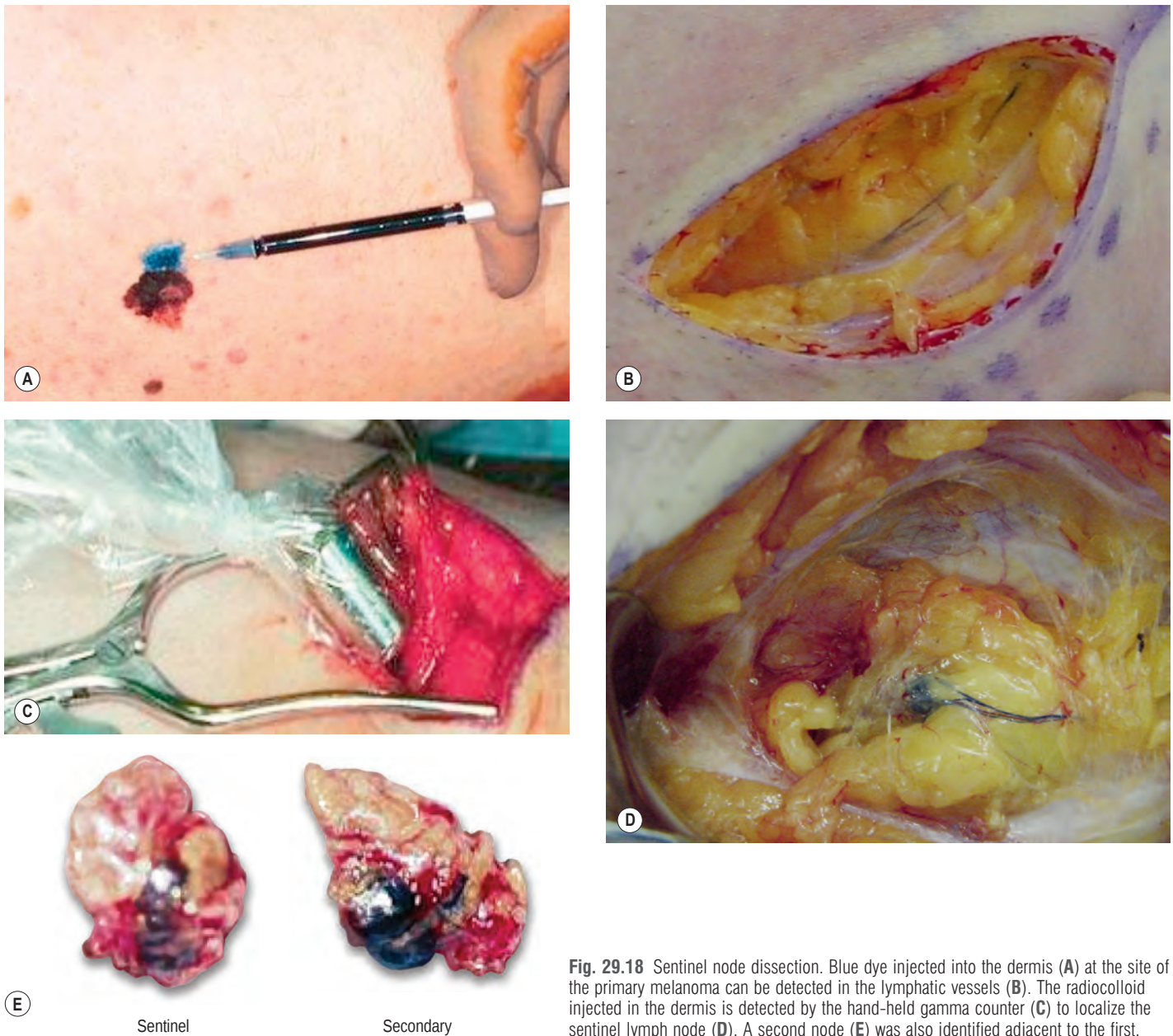


Fig. 29.18 Sentinel node dissection. Blue dye injected into the dermis (A) at the site of the primary melanoma can be detected in the lymphatic vessels (B). The radiocolloid injected in the dermis is detected by the hand-held gamma counter (C) to localize the sentinel lymph node (D). A second node (E) was also identified adjacent to the first.

very thick tumors (greater than 4 mm) because even though this group of patients has a 65–70% risk of distant metastases, the SLNB may still provide important prognostic information, and obviate a subsequent lymphadenectomy in a number of patients who would subsequently develop enlarged nodes.⁸⁶

Based on analyses of the AJCC Melanoma Staging Database, nodal status has been demonstrated as the overriding factor predicting disease outcome.^{87–89} For patients with clinically detectable nodal disease (macrometastases), the characteristics of the primary tumor essentially become irrelevant with respect to predicting five-year survival. That is, thickness, ulceration, and mitotic rate do not maintain statistical significance on multivariate analysis.⁹⁰ As the majority of patients present without clinically apparent nodal involvement, the goal of SLNB is to identify patients with microscopic nodal metastases as early as possible so they might benefit

from the early removal of these metastatic nodes before the disease can spread any further, and to consider these patients for adjuvant therapy. In patients with nodal disease (including those with nodal disease limited to micrometastases), it has been demonstrated that the most important prognostic factor is the *number of involved nodes*.⁹⁰

The node (N) category of the 2017 edition of the AJCC Melanoma TNM system (see Table 29.2), includes the following designations:

Nx: Nodes are not assessable (e.g., previously resected for other reasons)

N0: No regional lymphatic metastases.

N1: One involved lymph node.

N1a: clinically occult micrometastasis;

N1b: clinically detected macrometastasis

N1c: in transit or satellite metastasis without metastatic nodes

N2: Two to three involved nodes

N2a: clinically occult micrometastases

N2b: at least one node with clinically detected macrometastasis

N2c: in-transit or satellite metastasis with one metastatic lymph node

N3: Four or more positive nodes, matted nodes, or in-transit/satellite metastases with one or more positive nodes

N3a: clinically occult micrometastases

N3b: one clinically detected micrometastasis

N3c: two or more clinically detected micrometastases

The presence of in-transit metastases, or nodal involvement, classifies the patient as Stage III, with subclassification (IIIA, IIIB, IIIC, or IIID) dependent upon the extent of lymphatic disease (see [Table 29.3](#)).

Evaluation of systemic disease

The evaluation of the patient with malignant melanoma requires a complete physical examination of the primary site and regional draining lymph nodes to detect any clinical evidence of satellite or in-transit lesions (metastases) in the skin or of metastases to lymph nodes. The abdomen needs to be examined for evidence of an enlarged liver, enlarged spleen, or abdominal masses that would suggest intra-abdominal metastases. The extent of examination and the tests ordered for such evaluations are predicated on the stage of the primary diagnosis ([Table 29.6](#)). A chest radiograph may be indicated to look for pulmonary metastases, and computed chest tomograms may add to the detection of small and early lesions. Liver enzyme function tests are simple, sensitive, and reliable for detecting liver metastases and, when results are negative, may serve as a baseline for later annual follow-up examinations. Serum lactate dehydrogenase (LDH) has been identified as an important, independent prognostic factor in patients with disseminated melanoma. The AJCC Melanoma Staging Database included 7972 patients with distant metastases, and one- and two-year survival rates were significantly lower in patients with elevated serum LDH (32% versus 65% and 18% versus 40%).⁴⁶ Therefore, serum LDH must be measured at the time stage IV disease is documented, as it provides important prognostic information.

Computerized scans

Although tomographic radiographs of the lungs are helpful in detecting pulmonary metastases, computed tomographic (CT) scanning of the chest and abdomen does not offer a significant advantage as an initial screening test over chest radiographs and liver function tests.⁹¹ Even though this imaging technique requires skillful interpretation for optimal use, analyses have shown that screening chest radiographs, a much less expensive modality, are just as useful as CT scans in detecting metastatic lesions at the time of the initial diagnosis. However, CT scans do offer the potential for superior detection of metastatic lesions in various organs, and they are quite useful for evaluating the brain ([Fig. 29.19](#)).

Table 29.6 Staging evaluation: tests recommended for determination of presence and extent of tumor spread

Primary tumor (no clinical evidence of other involvement)

Physical examination

Chest radiography

Liver function tests

Lymphoscintigraphy to detect sites of sentinel nodes (if primary tumor is 1 mm or more thick)

Local and regional disease (in-transit lesions or nodal involvement)

Physical examination

Liver function tests

CT scans

of chest and abdomen (to examine lungs and liver)

of pelvis if tumor involves lower extremities

of neck if tumor involves the head and neck

Lymphoscintigraphy to detect sites of sentinel nodes

Additional scans as indicated by clinical signs or symptoms

Distant organ metastases

Physical examination

Liver function tests and serum lactate dehydrogenase level

CT scans as indicated above

MRI scans if required to detect extent of soft tissue invasion

PET scans to detect extent of tumor involvement of vital organs (lung, liver, brain)

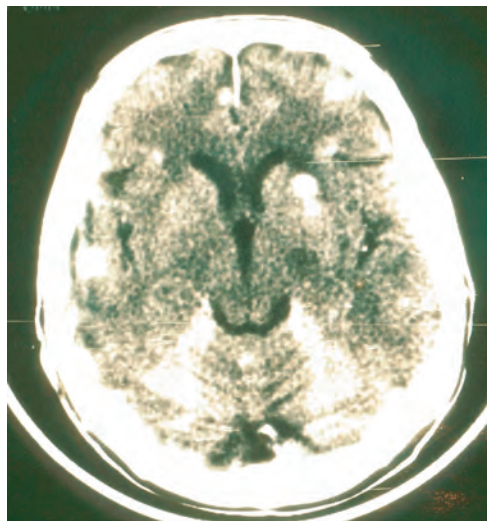


Fig. 29.19 CT scans of the brain can detect small lesions. In this patient, several lesions are identified in both hemispheres.

Whereas patients with primary melanomas thicker than 1 mm may be considered at moderate risk, those with lesions greater than 2 mm are considered at high risk for metastases. Patients with stage III disease are certainly candidates for intensive surveillance. These higher risk patients should be evaluated for distant organ metastases with chest and abdominal CT scans, which enable the physician to examine the lungs, the liver, and the spleen in one test. Enhanced brain CT scans should also be considered.

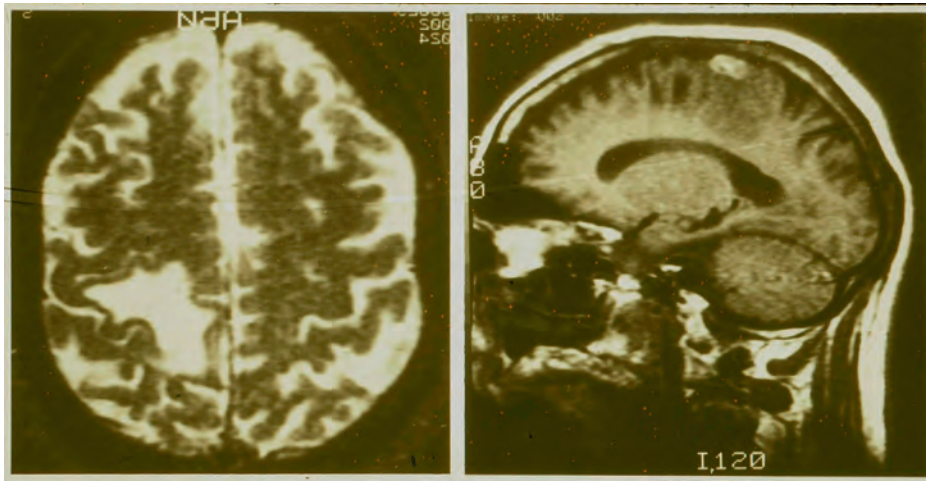


Fig. 29.20 Magnetic resonance imaging, in this case of the brain, demonstrates involvement of soft tissue by melanoma.

On the other hand, CT scans can be helpful for staging the disease in patients who present with local or regional extension of the disease. In some patients, the extent of the disease detected from the CT scans can be elaborated by the use of magnetic resonance imaging scans (Fig. 29.20). Positron emission tomography (PET) scan has been found to be valuable for evaluating patients for extension of their disease and assigning stage.^{92,93} The increased metabolism of the tumor is reflected in the increased uptake of radioactive-labeled glucose, which is represented by the brighter activity at the site of the metastases (Fig. 29.21). In the absence of infectious processes, the false-positive rate has been reported to be less than 5% with PET scans. The restrictions to the use of PET scans are the limited availability of the scanners and the greater expense for these studies.

M category of TNM system

The AJCC staging system categorizes patients with distant metastases according to the site(s) of disease involvement and the serum lactate dehydrogenase (LDH) level (see Table 29.2).⁴⁶ M1a, associated with the best prognosis, identifies patients with metastases limited to distant skin, subcutaneous or lymph node sites, and a normal (0), or elevated (1) serum

LDH. M1b denotes patients with lung metastases and a normal (0), or elevated (1) serum LDH. The patients with the worst prognosis are M1c, with metastases to other visceral (non CNS) sites, and M1d, with distant CNS metastasis (both also with a normal (0) or an elevated (1) serum LDH). With respect to staging (see Table 29.3), any M designation (i.e., the presence of any metastatic disease beyond the regional lymph nodes) places the patient in the Stage IV category.

While rare, patients will occasionally present with metastatic melanoma without an identifiable primary tumor. In these situations, if the patient has isolated metastases in the lymph nodes, skin, or subcutaneous tissues and an unknown primary, they are considered Stage III, as studies suggest they have a similar (or slightly better) survival rate compared to those with involved lymph nodes and a known primary tumor.⁹⁴⁻⁹⁸

Members of the AJCC Melanoma Task Force recently developed an electronic prediction tool for patients presenting with localized disease (<http://www.melanomaprognosis.net>). The prediction tool can be used to predict the 1, 2, 5 and 10-year survival rates from initial diagnosis (with a 95% confidence interval) for an individual patient based on his/her relevant clinical and pathologic information. The predictive models were developed and validated using a combined

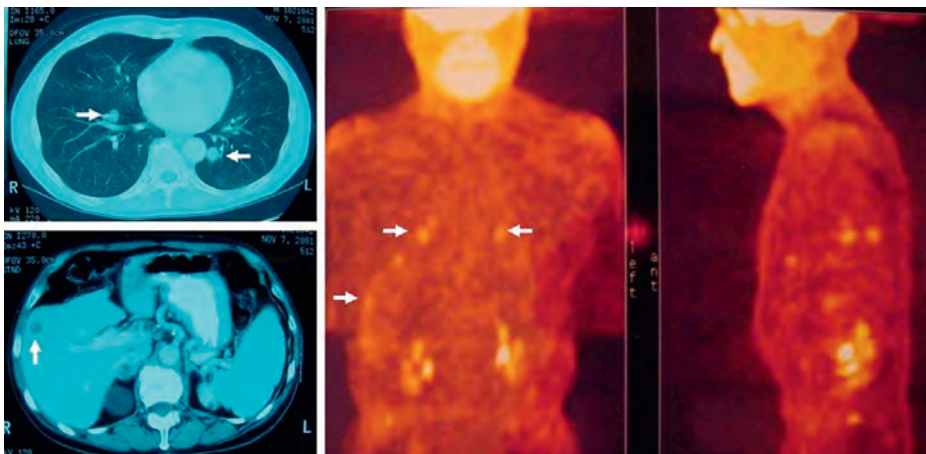


Fig. 29.21 PET scan of the chest and abdomen (right) confirms the increased activity of metastatic lesions seen on CT scan in the lung (upper left) and liver (lower left).

database (n=28047) from 11 major institutions and study groups participating in the development of the AJCC Melanoma Staging System.⁹⁹

Surgical considerations and treatment

Initial biopsy

Some clinicians have questioned the safety in biopsy of malignant melanoma for fear that tumor cells might be disseminated through the blood stream. To evaluate this risk, Epstein *et al.*²⁸ reviewed 170 melanoma patients from the California Tumor Registry over a 4-year period, 115 of whom underwent biopsy of the melanoma before surgical treatment and 55 of whom had not. The 5- and 10-year cure rates, as well as relative cure rates by life-table analysis to eliminate differences in the age distribution of the two groups, were more favorable for those patients who had undergone a previous biopsy. The results of this study suggest not that biopsies improve the overall cure rates but that an incomplete removal of a melanoma by a surgical biopsy followed by the definitive surgery does not decrease the cure rate. Additional studies have confirmed this observation, one from the United States with 230 patients¹⁰⁰ and a subsequent study from Denmark¹⁰¹ with 225 patients followed up for a minimum of 5 years. The role of biopsy type in relation to survival was specifically analyzed by Lederman *et al.*¹⁰² in 472 patients; 119 underwent incisional biopsy (either punch or incision) and 353 had an excisional biopsy. After controlling for other factors, especially tumor thickness, no statistically significant difference was demonstrated between patients in the different biopsy type groups. Importantly, biopsy of the lesion (incisional or excisional) will make the diagnosis of melanoma as well as demonstrate the aggressiveness of the lesion by the degree of invasion into the dermis.

Our recommendation, if the lesion is small, is to perform an excisional biopsy with a 1–2-mm margin of normal-appearing skin to permit the pathologist to render a diagnosis reliably and to determine the thickest depth of invasion. However, if functional or cosmetic concerns prohibit easy removal of the entire lesion, an incisional biopsy or punch biopsy is an acceptable alternative. The only drawback of such a partial biopsy is that the final therapeutic excision may show a lesion that is classified with greater depth of invasion than had been initially discovered. In some cases, the patient would have been eligible for sentinel node biopsy if the proper depth had been assessed before wide excision and resurfacing. We do not prefer shave biopsy, though it may be acceptable when the index of suspicion is low and the lesion is broad (e.g., broad shave biopsy in some cases of lentigo maligna and melanoma *in situ* may increase diagnostic sampling), or in cases of suspected subungual melanoma.

As specific details from the biopsy specimen will dictate the next steps in management, the specimen must be assessed by a pathologist with expertise in the evaluation of pigmented lesions. Pathologic details that must be reported include: Breslow thickness in millimeters, histologic ulceration, mitotic rate per mm², peripheral and deep margin status, and Clark level (for lesions ≤1 mm in depth). Other histopathologic details of potential significance include: microscopic satellitosis, regression, tumor infiltrating lymphocytes, neurotropism, and histologic subtype.

Wide local excision

The purpose of wide local excision (WLE) of melanoma is to decrease the incidence of local recurrence, reported in the literature to range from 3% to 20%. In large series, the highest risk of local recurrence has been documented with primary tumors on the hands and feet, with a recurrence rate of 11% to 12%, whereas the risk is only 5% to 6% for tumors on the face, scalp, and ear.⁶²

It has generally been accepted that melanomas less than 0.76 mm thick are uniformly curable, as reported by Breslow.⁶¹ Breslow and Macht¹⁰³ reported in a small series of 62 patients with lesions less than 0.76 mm that neither local recurrences nor metastases developed, regardless of the width of resection margin. Day *et al.*¹⁰⁴ reported that although thin lesions have a good prognosis, the prognosis may be worse when the melanoma is located within the BANS area, an acronym for the upper *back*, upper posterior *arm*, posterior *neck*, and posterior *scalp*. On the other hand, Woods *et al.*¹⁰⁵ reported 11 deaths among 400 patients with melanomas less than 0.76 mm treated at the Mayo Clinic; seven of the melanomas were not within the BANS area at all. In a smaller series, Briggs *et al.*¹⁰⁶ reported that 10% of the patients with melanoma less than 0.76 mm died during their 10-year experience.

The World Health Organization (WHO)¹⁰⁷ evaluated the importance of the width of resection of the primary melanoma and the surrounding normal skin in a study of 593 patients with clinical stage I disease. Curability was not influenced by the resection margins but decreased with increasing thickness of the primary melanoma. In a large study of more than 3400 patients, Urist *et al.*⁶² noted that the recurrence rate of 146 melanomas of the neck was less than 2% even though most of the patients (84% to 87%) were treated with resection margins of only 1–2 cm.

In a study of 598 patients with clinical stage I melanoma, the New York University–Massachusetts General Hospital Melanoma Clinical Cooperative Group noted that resection margins of 1.5 cm or less were associated with a significantly greater incidence of recurrences than were resection margins greater than 1.5 cm. However, margins greater than 3 cm did not lead to a lesser recurrence rate.¹⁰⁸ Indeed, for melanomas greater than 2 mm thick, retrospective data suggest that margins less than 2 cm may decrease the cure rates.^{62,109–111}

The thickness of the melanoma is the key factor in determining the recommended margin of normal tissue to be excised. However, a recent systematic review and meta-analysis of randomized controlled trials of surgical excision margins in melanoma did not demonstrate a statistically significant difference in overall survival between narrow or wide excision margins.¹¹² Nonetheless, recommended margins have decreased progressively as a result of multiple large clinical trials that have examined the impact of margins on local recurrence (Table 29.7).

With respect to *in situ* melanoma, while there are no data from randomized trials to define the optimal extent of surgical resection, retrospective data support the use of 0.5-cm margins.^{19,113} For invasive melanoma, we recommend the following excision margins, based on data from multiple studies of optimal resection margins for malignant melanoma.^{114–123} For patients with Stage IA melanoma (≤1.0 mm in thickness), wide excision with a 1.0-cm margin is recommended. For lesions of 1.01–2.0 mm in thickness, a 1–2-cm margin is

Table 29.7 Trials comparing margin width for cutaneous melanoma

Study; author; year	N	Median follow-up	Lesion thickness	Margins	Local recurrence (%)	10-year overall survival
WHO; Cascinelli N; 1998 ¹¹⁵	612	12 yr	0–1 mm	1 cm	3/186 (1.6)	87%
			1.1–2.0 mm	1 cm	5/119 (4.2)	
			0–1 mm	3 cm	1/173 (0.6)	
			1.1–2.0 mm	3 cm	2/134 (1.5)	
Swedish; Cohn-Cedarmark G; 2000 ¹¹⁸	989	11 yr	0.8–2 mm	2 cm	3/476 (0.6)	79%
				5 cm	5/513 (1)	76%
French Cooperative Group; Khayat D; 2003 ¹¹⁹	326	16 yr	<2.1 mm	2 cm	1/181 (0.05)	87%
				5 cm	4/185 (0.2)	86%
Melanoma Intergroup Trial; Karakousis CP; 1996 ¹²¹	468	8 yr	1–4 mm	2 cm	(2.1)	70%
				4 cm	(2.6)	77%
British Trial; Thomas JM; 2004 ¹²³	900	5 yr	≥2 mm	1 cm	15/453 (3.3)	Not reported
				3 cm	13/447 (2.9)	Not reported

(Sources: Sladden MJ, Balch C, Barzilai DA, et al. Surgical excision margins for primary cutaneous melanoma. *Cochrane Database Syst Rev.* 2009(4):CD004835 and Stone M. Initial surgical management of melanoma of the skin and unusual sites. In: Atkins MB, Weiser M, Tsao H (eds). *UpToDate*. 18.3 ed. Waltham, MA: UpToDate, Inc.; 2010.)

recommended, recognizing that a full 2.0-cm margin may be difficult to achieve in some areas of functional or cosmetic significance.¹²⁴ For lesions >2.0 mm in thickness, a margin of at least 2.0 cm is recommended.

In determining the extent of the operation, whether on the face or on the trunk, it is important to consider the impact of the scar on the patient's self-image. The Pigment Lesion Study Group of the University of Pennsylvania evaluated the extent to which patients were distressed by scars after melanoma resections.¹⁰⁸ The two factors that had a negative impact were the degree of surgical depression or indentation and the patients' preoperative perception of the scar to be expected. The actual scar length did not have as much of an effect as the

extent of depression of the scar. As such, skin grafts are acceptable for reconstructions of large resection sites, but they cause significant deformities (Fig. 29.22), which are usually avoided with flaps for coverage. The author has previously reported on the safety of coverage of these wounds with flaps.¹²⁵

Head and neck

Although the skin of the head and neck accounts for only 9% of total body surface area, 15–30% of all primary melanomas develop on the head and neck.^{126,127} High-risk melanomas of the face should be excised as outlined above and closed with



Fig. 29.22 Skin grafts provide adequate coverage for wide resections, but they can lead to significant deformities, as demonstrated in the infraorbital region (A) and scalp (B).

adjacent flaps. Although resurfacing the resection site with a skin graft is possible, the cosmetic results are not as acceptable as with a flap. A local or regional skin flap covers the wound with a far more satisfactory color match to the rest of the face than a distant flap (Fig. 29.23).

A difficult area to resurface is a surgical defect over the chin because this area requires skin that firmly adheres to the mandible, soft tissue for contour, and a good match of the skin flap to the remainder of the face. A distant flap simply does not provide a satisfactory color match. A wide excision of this area can be resurfaced satisfactorily with an advancement flap of the neck.

On occasion, the melanoma forms on the upper part of the cheek, requiring removal of skin from the lower eyelids. This

area cannot be resurfaced with a skin flap because it requires thin pliable covering. Resurfacing is best accomplished by employing a cheek advancement flap to cover most of the defect and a full-thickness skin graft to the eyelids. The best place to harvest this skin graft is from the ipsilateral or contralateral upper eyelid; the postauricular area may be an acceptable alternative.

In situations where tissue conservation is deemed necessary, frozen section analysis may be considered, but it does carry a risk of false negative report.¹²⁸ Additionally, while investigational, Mohs micrographic surgery may be considered in these situations, or when treating superficial lesions of large diameter (e.g., lentigo maligna). Large series report that Mohs surgery¹²⁹ may control the primary lesion, but



Fig. 29.23 Melanoma of the cheek (A) was treated with a wide excision of the primary site (B), a complete functional neck dissection (C), and coverage with a large cervicofacial myocutaneous flap incorporating the platysma muscle (D). One year postoperative photographs (E,F).

longer follow-up is required before widespread adoption of this technique.¹³⁰ Treatment of lentigo maligna with imiquimod has also emerged as an effective therapy.^{131–134} Recent published work has shown the effectiveness of treating residual *in situ* melanoma at the margins of surgical resections with imiquimod, confirmed with negative biopsies after adequate treatment.¹³⁵

Extremities

Thin melanomas of the fingertips may be excised and the defect reconstructed with volar advancement flaps (Fig. 29.24) to provide sensate coverage. Melanomas of the nail bed that are thin can be removed with the underlying periosteum (Fig. 29.25A,B); if the tumor has not penetrated through the periosteum, then the distal phalanx can be saved and covered with a full-thickness skin graft. Lesions of the finger thicker than 1 mm are more safely treated with an interphalangeal joint amputation (Fig. 29.26) or a ray amputation, depending on the extent of the tumor. Subungual melanoma of the fingers should be resected at the distal interphalangeal joint to preserve function.¹³⁶ Similarly, subungual melanomas involving the toes should be managed with digital amputation at the metatarsal-phalangeal joint.

Melanomas of the dorsum of the hand, the forearm, and the leg may be treated more readily with a wide excision. These surgical wounds have traditionally been covered with skin grafts with good success. However, coverage of these wide excisions with local flaps (Fig. 29.27) has been accomplished with successful control of the primary site and a more cosmetically acceptable result.¹²⁵ Furthermore, these patients do not need to have the arm or leg immobilized, and they have a shorter hospital stay than do those who have had skin grafts.

Melanomas of the toes and feet are usually of the acral lentiginous type. These tumors spread aggressively and have a high incidence of local and regional recurrences. Therefore, they are best treated by aggressive resections (Fig. 29.28). A significant advantage to the use of flaps in the lower extremity is that patients may be able to ambulate the day after surgery and leave the hospital much sooner than patients treated with skin grafts.

Trunk

Primary melanomas of the trunk may be excised with more liberal margins (as much as 2–4 cm if need be) and still be closed easily. Some areas may be closed by wide undermining and large advancement flaps. Otherwise, these areas may still be closed readily by one or more local flaps (Fig. 29.29). Deep fascia and muscle may be preserved if not involved by tumor invasion.

Lymphadenectomy

The decision to perform a lymphadenectomy in a patient with melanoma requires further thought. In patients who present with palpable lymphadenopathy, it is appropriate to confirm diagnosis with fine needle aspiration, core needle, or open biopsy of the clinically enlarged lymph node(s). In the absence of radiological evidence of distant metastases, wide excision of the primary site and complete dissection of the involved lymph node basin is indicated. For staging purposes, the number of positive nodes, the total number of nodes examined and the presence or absence of extranodal tumor extension must be recorded.¹²⁴ Of note, in the lower extremities, when PET or pelvic CT scans reveal iliac and/or obturator lymphadenopathy, or if a positive Cloquet's

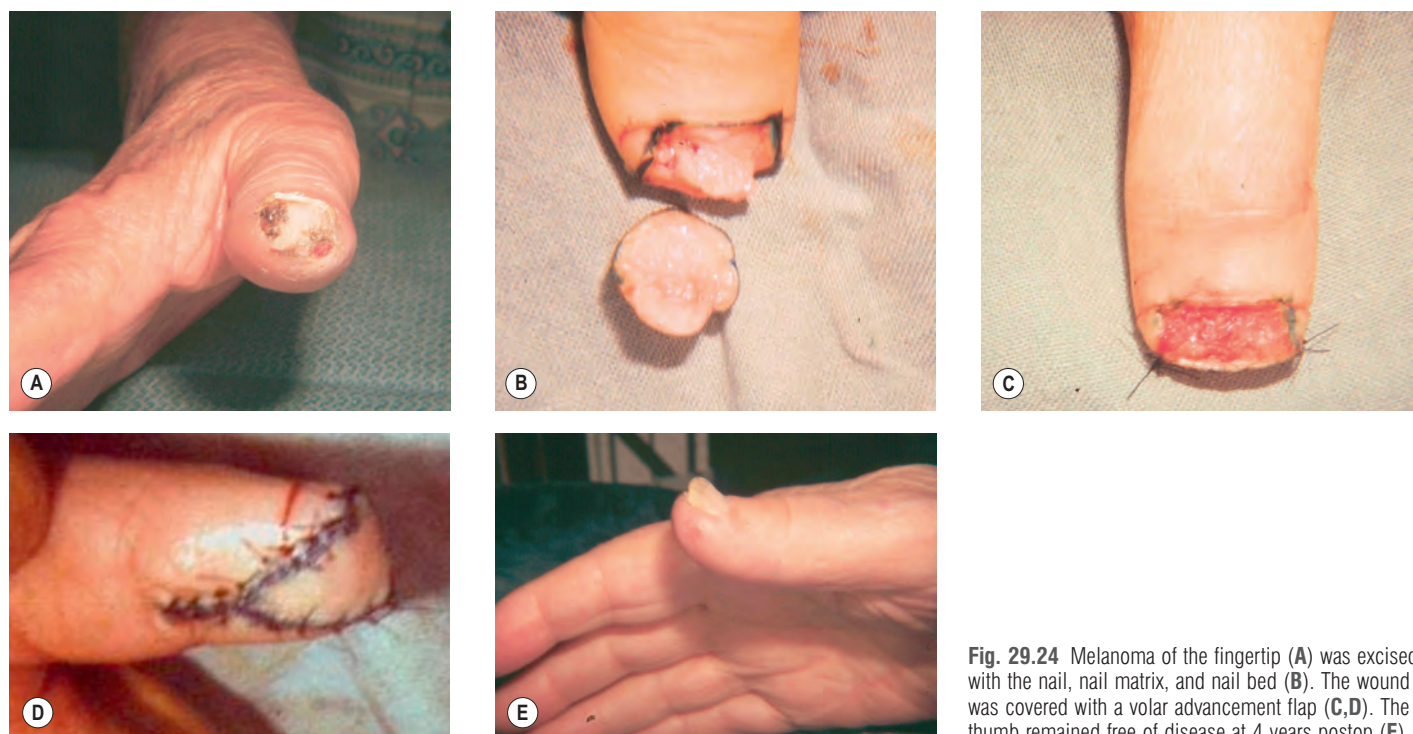


Fig. 29.24 Melanoma of the fingertip (A) was excised with the nail, nail matrix, and nail bed (B). The wound was covered with a volar advancement flap (C,D). The thumb remained free of disease at 4 years postop (E).

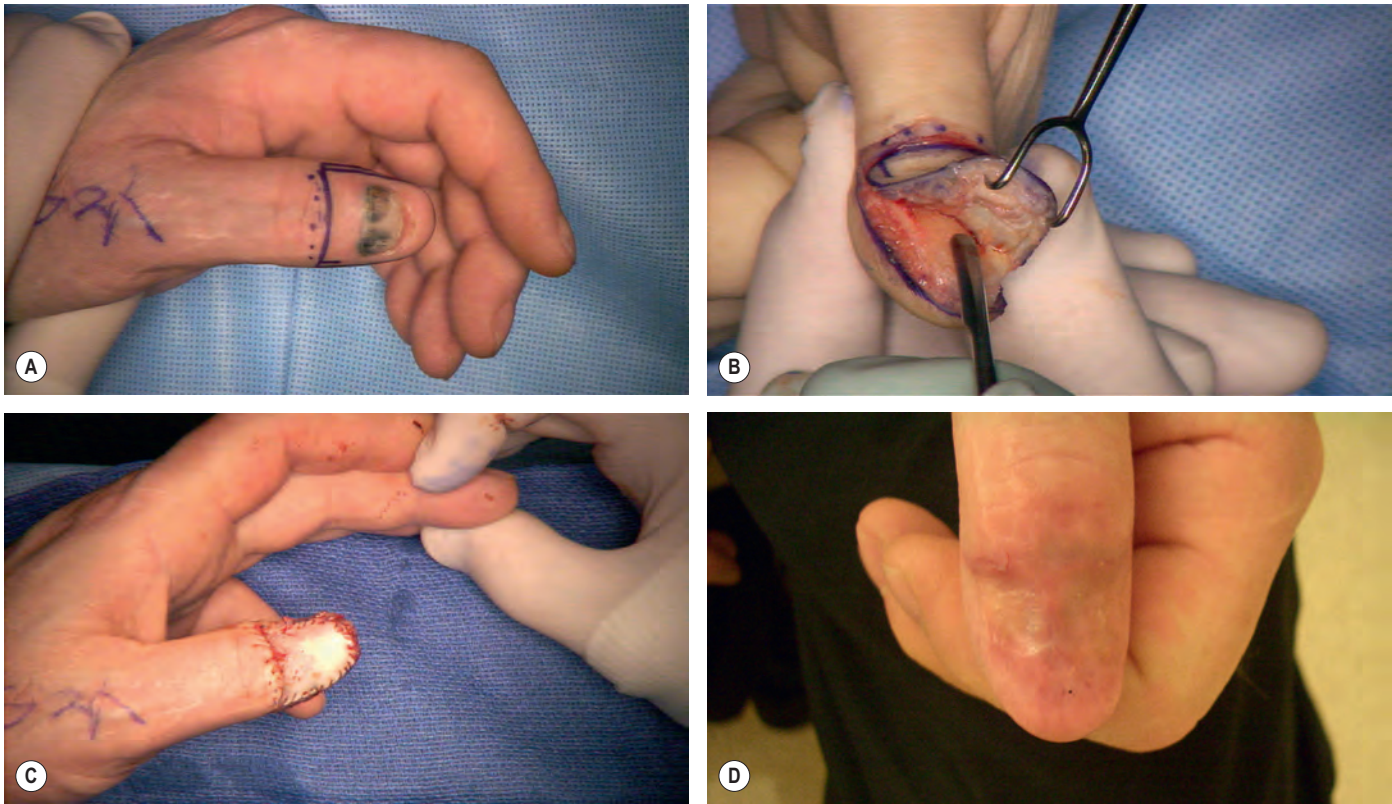


Fig. 29.25 (A) Thin melanoma of the nail bed. (B) Nail bed and eponychium is removed with the underlying periosteum. (C) Full-thickness skin graft. (D) Healed thumb nail bed.

lymph node is found, deep groin dissection should be considered.^{137,138}

The majority of patients, however, will present without clinical evidence of nodal disease, and some will require sentinel lymph node biopsy (for staging purposes). The decision regarding which patients should undergo SLNB is dependent upon the pathological stage of the primary lesion. As stated previously, SLNB should be considered for patients with primary melanomas that demonstrate aggressive biology. Specifically, this includes stage IA melanomas with adverse prognostic features (i.e., thickness ≥ 1.0 mm, positive deep margins, lymphovascular invasion, or young patient age), stage IB and II melanomas, as well as patients with resectable solitary in-transit stage III melanoma.¹²⁴ The decision regarding whether to proceed with SLNB is ultimately up to the patient and the treating physician, and should be performed at the time of WLE.¹²⁴

If the sentinel lymph node is negative, regional lymph node dissection is not indicated. If the SLN is positive, the patient should be offered complete dissection of the involved lymph node basin; 15–20% of these dissections will demonstrate melanoma in non-sentinel lymph nodes.^{139,140} It has been shown that factors related to the SLN can help predict the presence of melanoma in non-SLNs: size of the metastatic focus, number of metastatic foci, and extracapsular extension.^{141,142} Of note, these stage III patients should be considered for adjuvant treatment with interferon alfa, especially if they lack any serious comorbidity and have an otherwise reasonable life expectancy.

The Multicenter Selective Lymphadenectomy Trial (MSLT) was a large trial designed to address the role of lymphatic mapping with SLNB in determining prognosis and its impact on survival; the third of the five planned interim analyses was published in 2006.¹⁴³ The primary study group included 1347 patients with intermediate thickness melanomas (1.2 to 3.5 mm) who were randomly assigned to WLE with observation or WLE with lymphatic mapping and SLNB. In the observation group, if palpable nodal metastases became evident, the patient underwent completion lymphadenectomy. Likewise, in the SLNB group, if the SLNB was histologically positive, the patient underwent immediate completion lymphadenectomy. A survival benefit was not demonstrated for the overall study population randomly assigned to lymphatic mapping and SLNB. However, amongst the patients who had nodal disease, the patients in the observation group who subsequently developed nodal metastases had more involved nodes at the time of lymphadenectomy (3.3 vs. 1.4 nodes), and a significantly lower 5-year survival rate (52.4% vs. 72.3%). Nevertheless, the final report of the MSLT was published in 2014. There was no significant difference noted in the 10-year melanoma specific survival in the two groups in the study population where 20.8% were found to have nodal metastases and 79.2% had no metastases.¹⁴⁴

However, there is no place for the simple excision of the involved palpable lymph node alone because it is more than likely that additional lymph nodes have micrometastases.¹⁴⁵ This question will be answered by the MSLT-II trial in progress now. In the meantime, the only accepted treatment is a

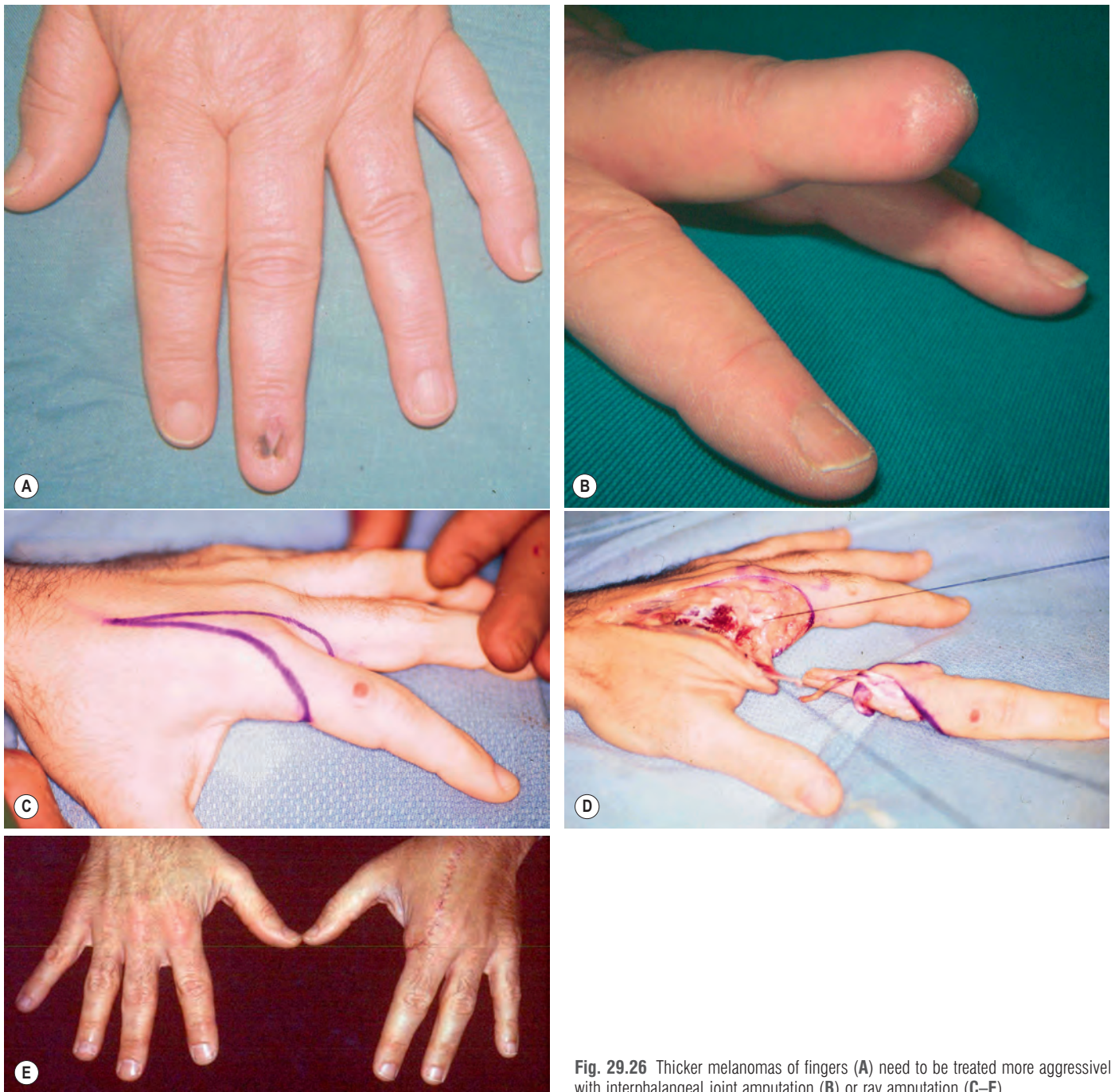


Fig. 29.26 Thicker melanomas of fingers (A) need to be treated more aggressively with interphalangeal joint amputation (B) or ray amputation (C–E).

complete lymphadenectomy of the regional group of lymph nodes.

Cervical lymphadenectomy

Patients with melanoma of the face and anterior scalp (Fig. 29.30) who are selected for cervical lymphadenectomy because of positive sentinel lymph nodes should also be considered for superficial parotidectomy on the ipsilateral side because the preauricular lymph nodes are the first echelon of nodal drainage. A cervical lymphadenectomy (Fig. 29.31) can be performed with or without preservation of the spinal

accessory nerve, internal jugular vein, and sternocleidomastoid muscle to provide a more acceptable appearance and functional neck and shoulder muscles.¹⁴⁶

Axillary lymphadenectomy

The patient is placed in the supine position with the arm abducted and placed freely on two arm boards. The entire arm, including the hand, is prepared for surgery and draped, so that the arm can be moved as needed during the procedure. Make a prominent S-shaped incision with the midportion placed transversely across the apex of the axilla, with one limb



Fig. 29.27 Wide excisions of melanomas of the hands, forearms, and legs (A) may be treated with local transposition flaps (B) to allow the patient to use the extremities early in the postoperative period (C).

descending behind the anterior edge of the lateral border of the pectoralis major muscle (Fig. 29.32) and the second limb descending along the posterior border of the upper arm. Elevate the two opposing skin flaps at the level of Scarpa fascia to expose the axillary contents.

Identify the brachial vein along the arm and dissect proximally to the axilla, from the anterior portion of the upper arm toward the posterior portion. Dissect the entire axillary contents in this fashion, moving in a distal to proximal direction. Ligate and transect the branches of the brachial vein; leave the thoracodorsal artery, vein, and nerve intact, however.

Dissect the axillary contents from along the lateral border of the pectoralis major muscle, leaving the muscle fascia behind with the muscle. Free the contents from the posterior surface of the pectoralis major, which is then retracted to expose the pectoralis minor. Dissect the fat and lymphatic contents from behind both the pectoralis major and minor muscles and retract this material downward. Using a surgical sponge pad, sweep the axillary contents away from the chest wall in a caudad direction. This maneuver usually exposes the long thoracic nerve along the chest wall. Preserve this nerve.

After the axillary contents are removed, reposition the skin flaps and suture them closed over large suction catheters. These catheters remain in place for 3 to 10 days, depending on the amount of 24-hour drainage accumulated. The decision to remove the drain should be based on the pattern and rate of daily decrease in the drainage rather than the actual amount. The drains are most commonly ready to be removed by the fifth or sixth day. The patient is instructed to keep the arm in a sling during waking hours to decrease shearing forces on the dissected tissues and thereby lessen the drainage.

Pelvic and inguinofemoral lymphadenectomy

Excision of inguinofemoral lymph nodes is facilitated by a horizontal incision along the skin crease 2 cm above and parallel to the inguinal region and a vertical incision over the femoral vessels, beginning in the inguinal skinfold and extending inferiorly for 8 to 10 cm. This approach results in an “interrupted” T incision (Fig. 29.33). Carry the skin incision in the inguinal area down to the fascia of the external oblique muscle and split it open to expose the internal oblique muscle. Dissect this origin of the internal oblique muscle sharply off

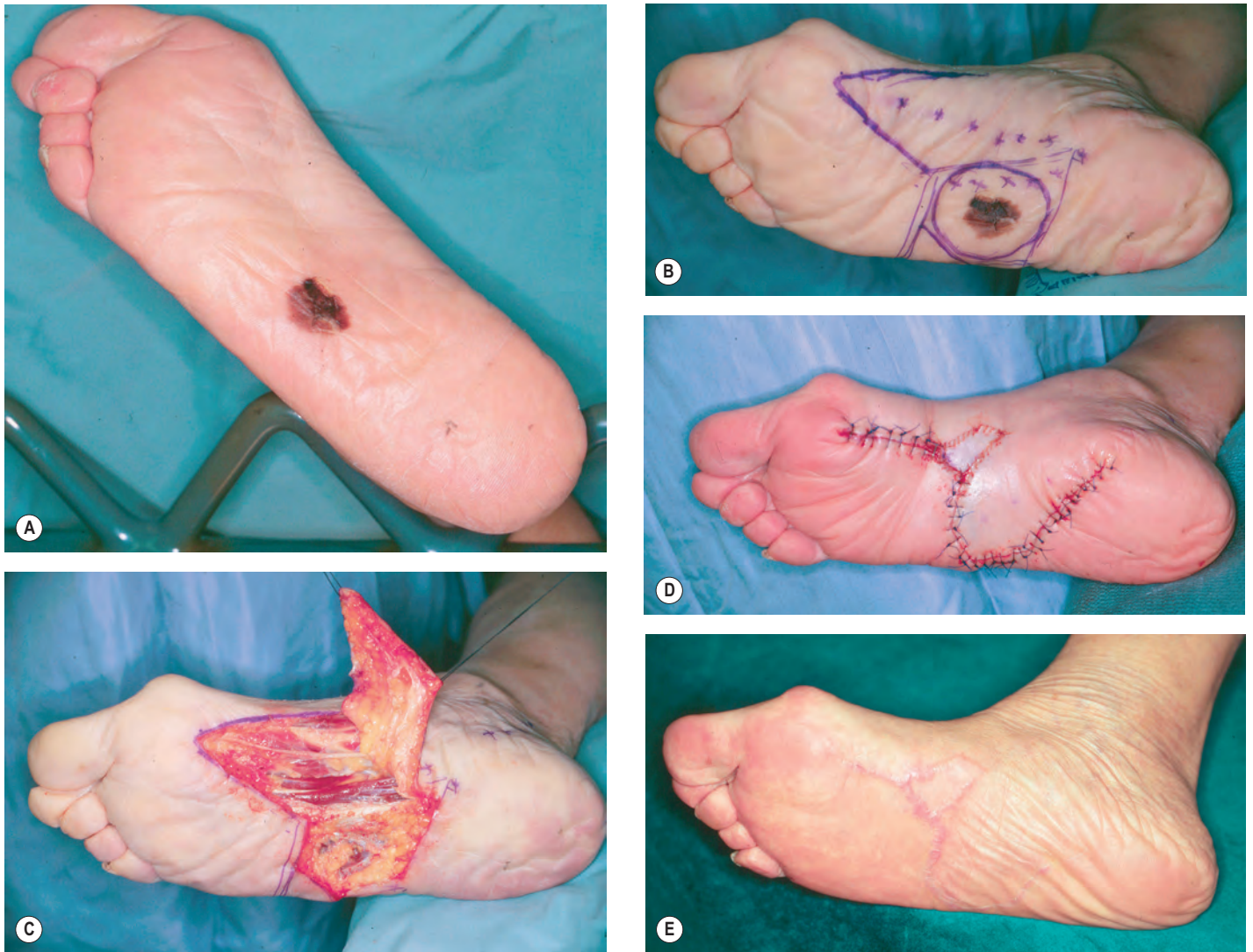


Fig. 29.28 Melanoma of the plantar area (A) may be resurfaced with an arterial fasciocutaneous flap (B–E).



Fig. 29.29 In the truncal area, deep melanomas may be resected widely (A) and still be closed reliably with large transposition flaps (B).

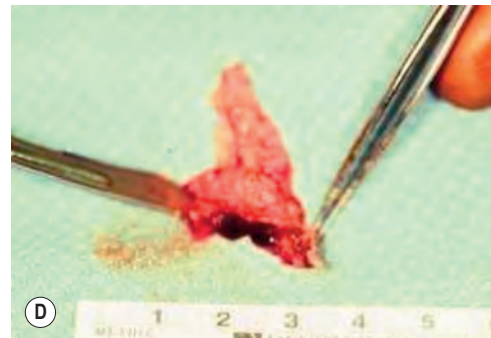
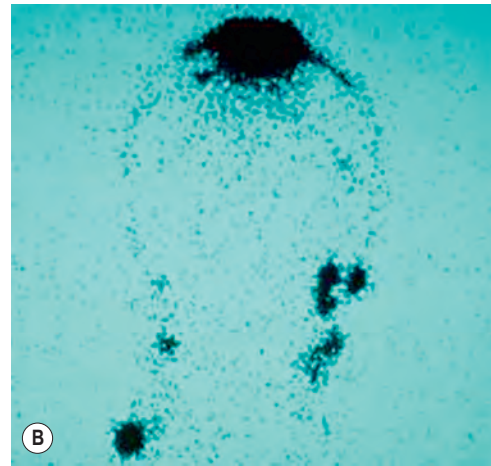


Fig. 29.30 Melanoma of the vertex of the scalp (A) was found to have lymphatic drainage to bilateral parotid and cervical nodes (B). The parotid sentinel node (C) was found to be positive (D). Postoperative healed flaps (E).

the iliac crest to provide access to the retroperitoneal space. Pull the peritoneum away along the undersurface of the transversalis fascia from the external iliac vessels and lymph nodes. This provides an excellent view of the nodes for the pelvic lymphadenectomy.

Elevate the skin flaps on either side of the femoral incisions at the level of Scarpa fascia as well as the skin below the horizontal incision (Fig. 29.34). Elevate the skin completely from the inguinal incision to the lower end of the femoral incision. Dissect the femoral fat and lymphatic tissues down to but not including the muscle fascia. Continue the dissection cephalad

on the surface of the muscle fascia until the saphenous vein and saphenous bulb are reached on the femoral vein.

Dissect the contents in the inguinal region down to the fascia of the external oblique muscle and in the caudad direction to communicate with the femoral dissection. Do not remove the muscle fascia or transpose the muscles adjacent to the femoral vessels to cover these vessels; such procedures increase the risk of lymphedema. Close the wounds over large suction catheters that remain in place for 3 to 10 days. Patients are permitted to ambulate the night of surgery or the next morning.

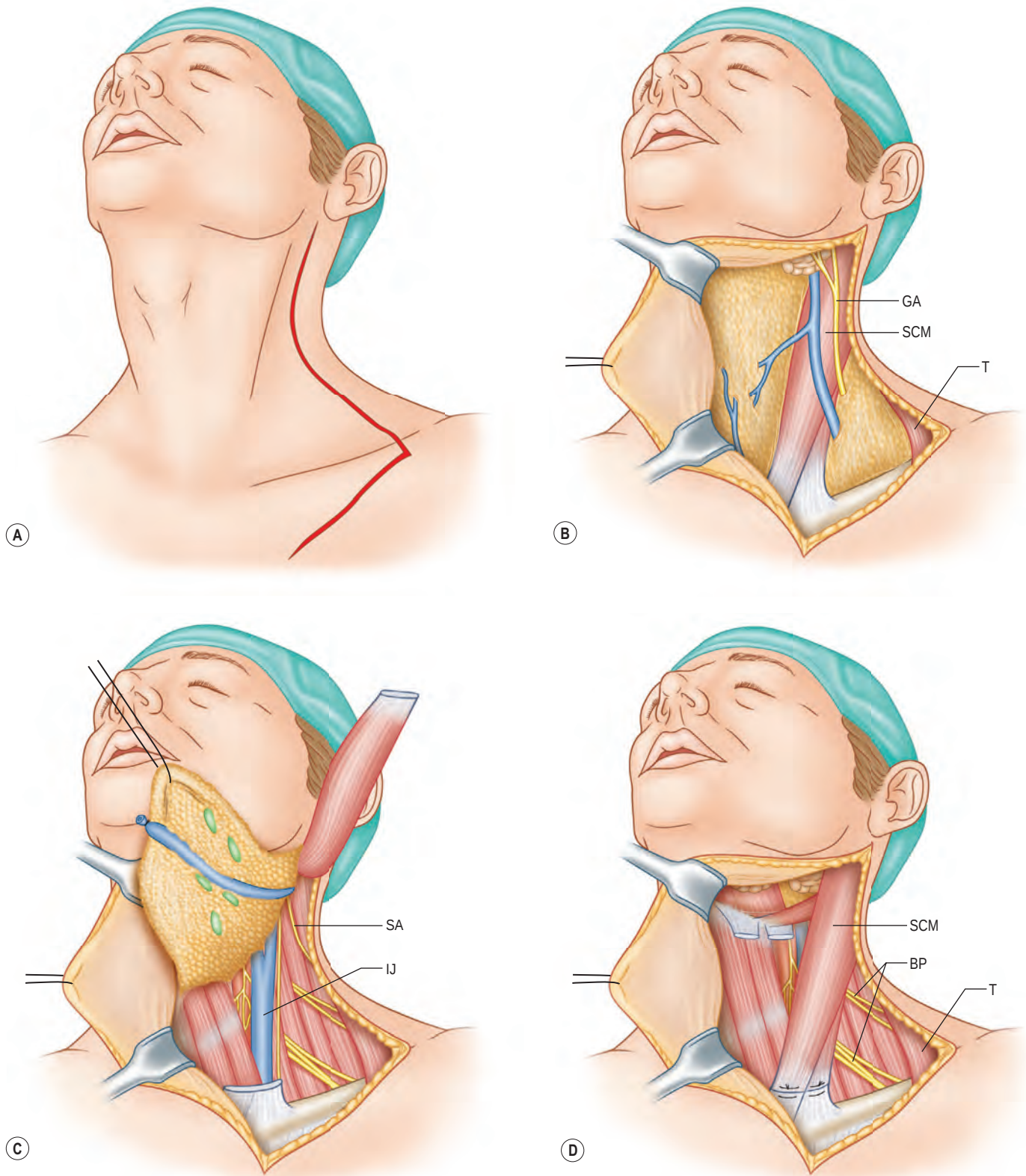


Fig. 29.31 Functional radical neck dissection can be performed while preserving the sternocleidomastoid muscle (SCM), the internal jugular vein (IJ), and the spinal accessory nerve (SA). BP, brachial plexus; GA, great auricular nerve; T, trapezius. (Reproduced from Ariyan S. *Radical neck dissection*. Surg Clin North Am. 1986;66:133.)

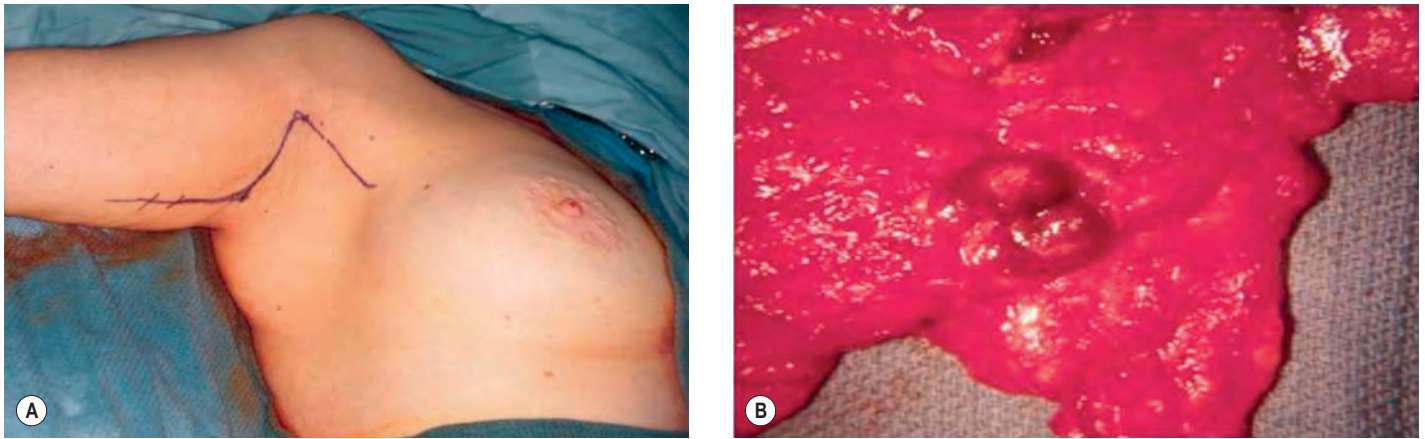


Fig. 29.32 Axillary incision is S shaped (A) to provide opposing flaps for greater access to the axillary contents (B). See text for details.

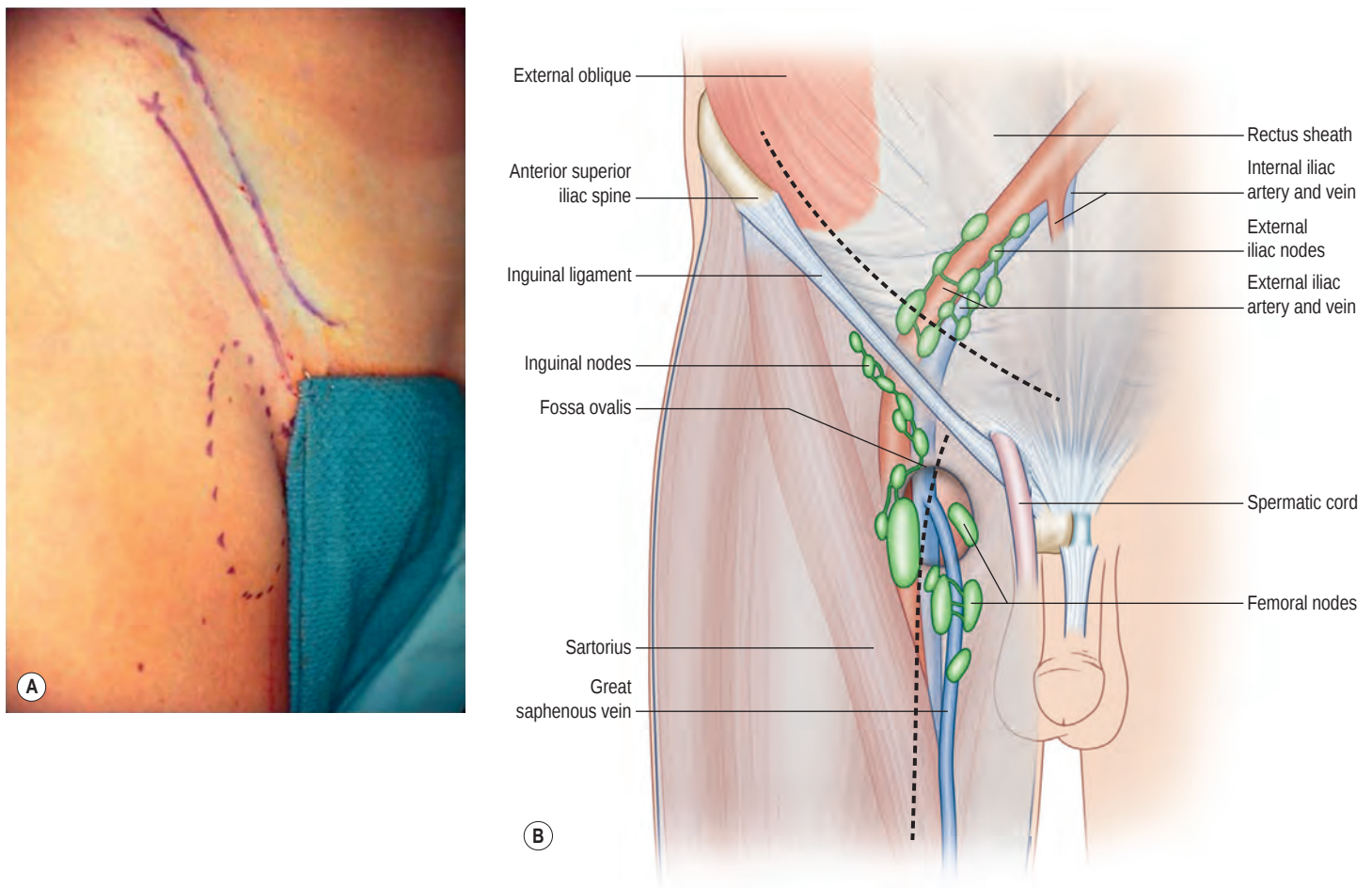


Fig. 29.33 An "interrupted" T incision (A,B) is used for access to both the inguinal and iliac nodes.

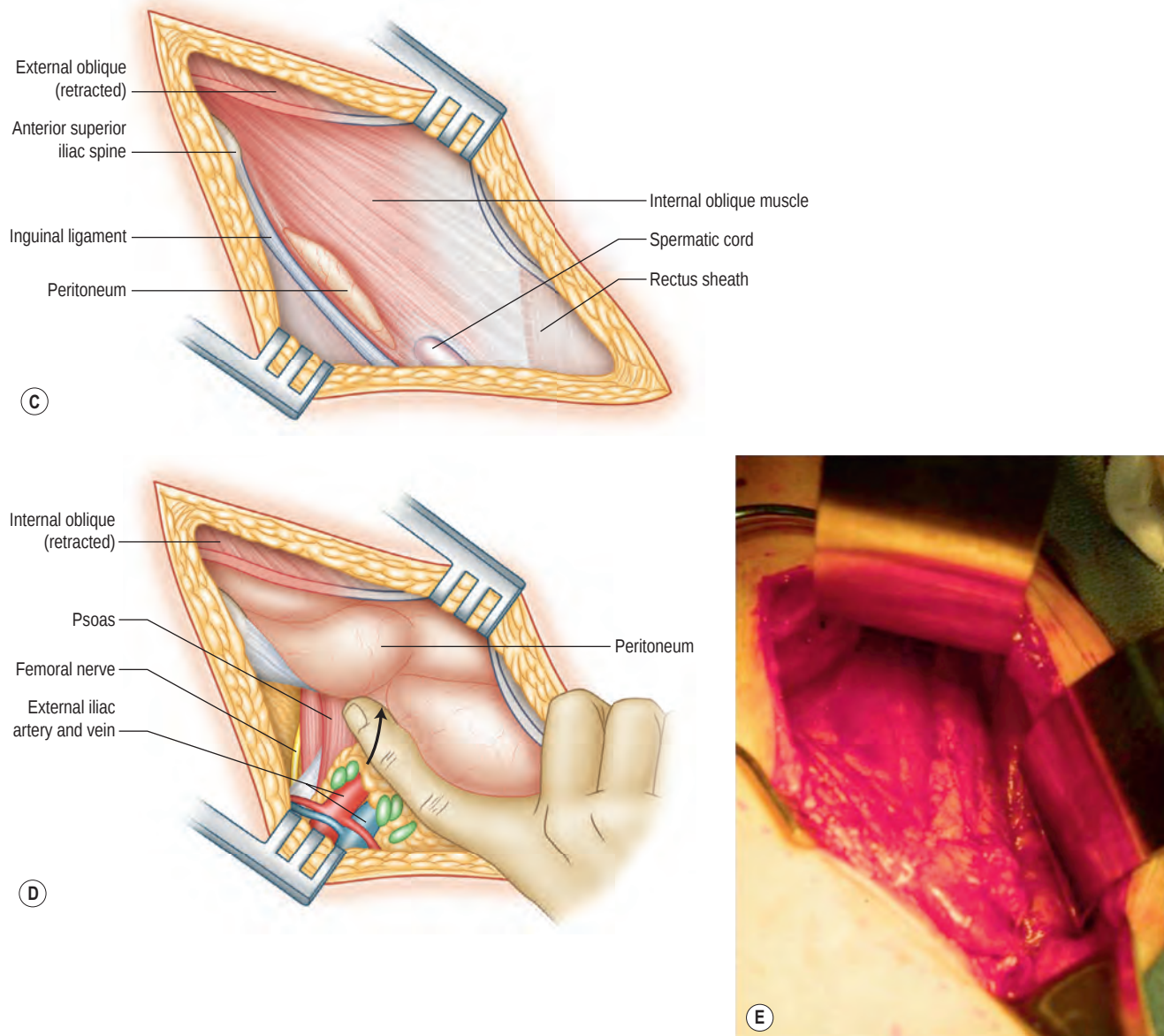


Fig. 29.33, cont'd The fascia of the external oblique muscle is split (C), and the internal oblique and transversalis are dissected away from the inguinal ligament and iliac crest. The peritoneum is peeled back by finger dissection (D) to obtain retroperitoneal access to the iliac and obturator nodes (E).

Adjuvant treatment for melanoma

Wide local excision is the standard of care for early stage melanoma, and the majority of patients present with stage I–IIA disease. However, high-risk patients with stage IIB–III disease have a generally poorer prognosis. These patients have been the primary focus in development of adjuvant therapies for melanoma. Over the past 30 years, a number of efforts with chemotherapeutic agents (e.g., dacarbazine¹⁴⁷), nonspecific immune adjuvants (e.g., BCG vaccine¹⁴⁷), and hormonal agents (e.g. megestrol acetate), have not demonstrated a benefit over observation or placebo. The most promising results have been demonstrated with interferon alfa (IFN- α), an immune modulator that can induce antitumor activity.

Interferon alfa

Early clinical studies with IFN- α demonstrated modest anti-tumor activity in patients with metastatic melanoma. A series of clinical trials were then started to examine the role of adjuvant IFN- α in patients with high-risk melanoma. Each of these trials has different doses and schedules, and an optimal approach to the administration of IFN- α has not been established. Review of data combined from multiple randomized controlled trials demonstrates that IFN- α is associated with an improvement in relapse-free survival but not with overall survival.¹⁴⁸ The role for adjuvant IFN- α for patients with intermediate to high-risk melanoma remains undefined.¹⁴⁹ Treatment with adjuvant IFN- α should be made on an individual basis, after discussion with the patient, with discussion of the potential benefits and side effects associated with IFN- α .

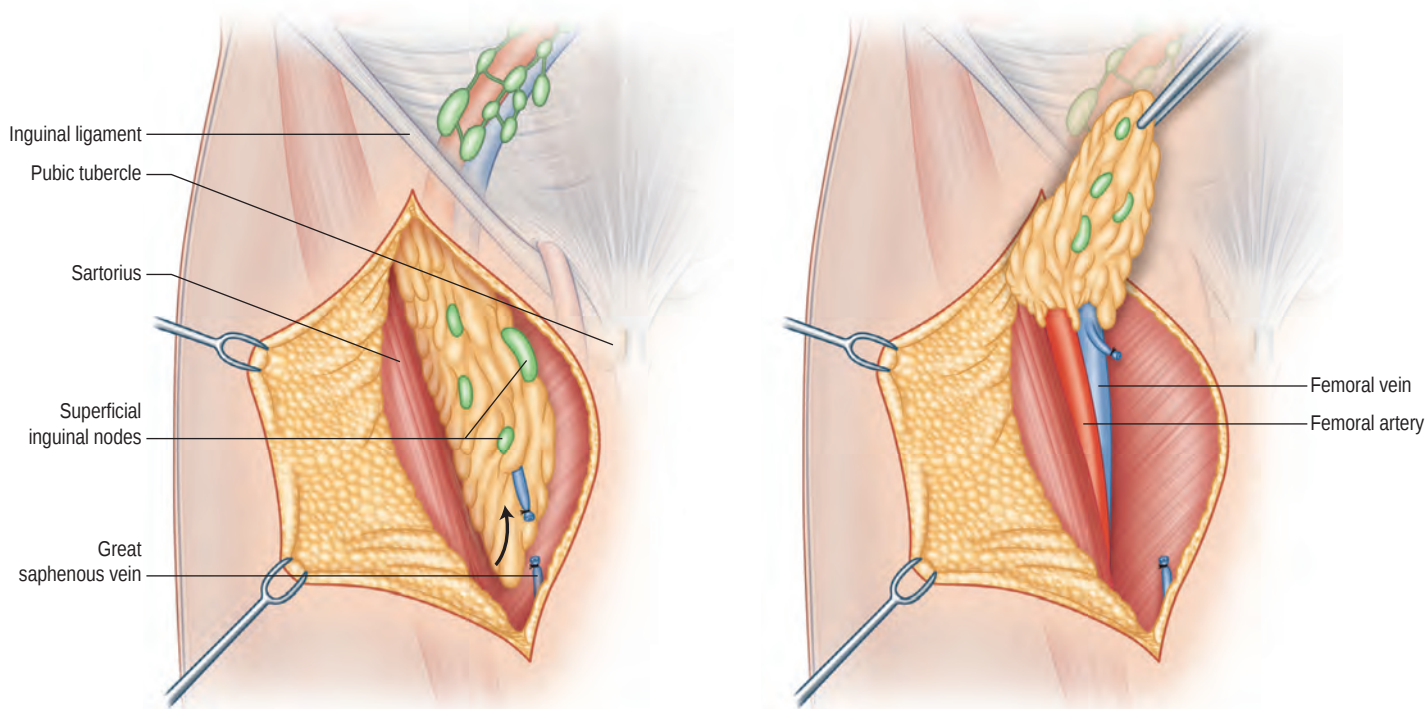


Fig. 29.34 The femoral nodes are approached through a vertical incision over the region of the femoral vessels. After the medial and lateral flaps are elevated (left), the subcutaneous fat containing the lymph nodes is dissected off the deeper muscle fascia (right).

therapy.¹⁵⁰ For patients with stage IIB through stage III disease which has been resected, the National Comprehensive Cancer Network (NCCN) recommends consideration of adjuvant treatment with IFN- α or enrollment in a clinical trial.¹²⁴

Radiation therapy

When excision of a primary melanoma with appropriate margins is not possible, adjuvant radiation may be considered, though it is not generally recommended for the primary treatment of cutaneous melanoma. In some exceptional circumstances, for patients who are poor candidates for surgical resection, radiotherapy may offer an acceptable alternative for control of disease. Additionally, successful treatment of ocular melanoma with eye and vision preservation is one of the major triumphs of radiation oncology. Very high rates of local control can be achieved with particle radiation treatment or episcleral plaque brachytherapy.¹⁵¹

Early studies by Barranco *et al.*¹⁵² demonstrated that cultured malignant melanoma cells differ from other types of tumor cells in their radiosensitivity. They found that the relative radioresistance of melanoma could be overcome by increasing the individual dose fraction. These studies helped form the basis for clinical practice, and subsequent studies helped to determine the ideal fraction size and total therapeutic dose that effectively treats melanoma.

In patients with extensive facial lentigo maligna melanoma that precludes adequate surgical resection based on functional or cosmetic considerations, radiotherapy has been reported.¹⁵³ However, more recent advances in topical therapies such as imiquimod (Aldara®), are supplanting radiation therapy (RT) in the non-surgical treatment of lentigo maligna melanoma.

Early work by Habermalz and Fischer demonstrated some success with higher-dose radiotherapy over more frequent time intervals than conventional radiotherapy, with partial or complete regression especially seen with subcutaneous metastases.¹⁵⁴ Prospective nonrandomized clinical trials at M.D. Anderson Cancer Center, treating high risk groups of melanoma patients with radiation therapy, have helped establish the basis of treatment with hypofractionated radiation therapy in melanoma.¹⁵⁵ While locoregional control was improved with adjuvant radiation, distant metastases developed in a large number of patients (58 of 174 patients).¹⁵⁵ Later studies from this group evaluated the outcome of patients with clinically apparent cervical lymph node metastases from malignant melanoma managed with surgical resection and adjuvant radiation.¹⁵⁶ After 10-year follow-up, the group demonstrated a 94% regional control rate. Radiation-related complications for the patients were manageable.¹⁵⁶ The same group evaluated the utility of radiation therapy alone in the treatment of 36 patients with positive SLNB (in lieu of completion lymphadenectomy), and demonstrated 93% regional control over five years.¹⁵⁷ However, when recurrences present within radiated fields, the surgical management can be arduous and lead to breakdown and non-healing wounds.

Work from Australia and New Zealand, including the Trans Tasman Radiation Oncology Group, has provided the most meaningful data with respect to the role of adjuvant radiation therapy in the treatment of metastatic disease.¹⁵⁸ In a prospective study, 250 patients with positive lymph nodes deemed to be at high risk for locoregional recurrence were randomly assigned to radiation therapy (48 Gy in 20 fractions) or observation. Patients were considered high risk if there was extracapsular extension, multiple positive nodes

(≥ 1 parotid, ≥ 2 cervical or axillary, or ≥ 3 groin-positive nodes), and large lymph nodes (≥ 3 cm for parotid, neck, and axilla, and ≥ 4 cm for groin location). After a median follow-up of 40 months, the radiation arm showed a significantly lower rate of lymph node recurrence as compared with observation. However, there were no differences in relapse-free survival or overall survival.¹⁵⁹ An update presented at the American Society of Clinical Oncology 2013 meeting with 6-year median follow-up confirmed these findings. The 5-year local recurrence rate was 18% for the RT arm and 33% for the observation arm ($P < 0.02$), and no difference in relapse-free or overall survival.¹⁶⁰

The NCCN recommends consideration of adjuvant radiation therapy for patients with multiple positive lymph nodes, lymph nodes with extracapsular spread, nodal recurrence and in-transit metastases. Additionally, radiotherapy should be considered after excision of primary melanomas that demonstrate neurotropism (desmoplastic type),¹⁶¹ as well as mucosal melanomas, which may or may not be amenable to complete excision.^{162,163} Radiation therapy may also be used for palliative treatment of melanoma distant metastases. It is effective for pain, mass effect, tumor-related hemorrhage, and local irritation from skin and subcutaneous metastases.¹⁶⁴

Isolated limb infusion/perfusion

Tumor recurrences correlate with the thickness of the lesion. Between 60% and 70% of recurrences appear in the first 18 to 24 months after surgical treatments (Table 29.8; Fig. 29.35).¹⁶⁵ It is presumed that the earliest recurrences are to local or regional lymph nodes, followed by in-transit metastases; distant metastases appear last.

Patients with local recurrences may be treated with wider surgical resections, but extensive local recurrences or in-transit metastases are more difficult to treat. In-transit metastases of extremities may be treated with isolation-perfusion of that extremity with melphalan,¹⁶⁶ dacarbazine (DTIC),¹⁶⁷ cisplatin, or hypo-osmolar perfusions with carboplatin.¹⁶⁸ Carboplatin eradicated the lesions after perfusion in some patients (Fig. 29.36), whereas the control was temporary in other patients. The advantage of DTIC is its low incidence of hepatic and systemic toxicity, which is far less than that after perfusion with L-phenylalanine mustard. Indeed, we found that such

perfusions were tolerated well among our elderly patients, with no greater risk of complications in this group than in our younger patients (Table 29.9).¹⁶⁹ In general, the major role for isolated limb infusion/perfusion is palliation of unresectable limb disease.

Table 29.8 Timing of recurrent melanoma after surgical treatment

Site	18 months	24 months	3 years	5 years	10 years
Nodal	63%	74%	86%	93%	95%
Local	55%	67%	81%	88%	95%
In-transit	55%	67%	80%	90%	97%
Systemic	40%	52%	71%	83%	95%
Overall	57%	97%	81%	90%	95%

(Modified from Fusi S, Ariyan S, Sternlicht A. Data on first recurrence after treatment for malignant melanoma in a large patient population. *Plast Reconstr Surg.* 1993;91:94.)

Table 29.9 Perfusion complications*

Age	20s	30s	40s	50s	60s	70s	80s	Total
Number	4	7	11	9	16	14	6	67
Edema (pre/post)			1		2	2	1	6
Edema (post)	1		2		2			5
Seroma	1		1		1	1		4
Wound			1		5	1	2	9
Pulmonary embolus					1			1
Total	2	0	2	2	9	2	2	19
	14/47 (32%)				4/20 (20%)			

*67 perfusions in 60 patients, 1976–1995. (From Ariyan S, Poo WJ. The safety and efficacy of isolated perfusion of extremities for recurrent tumor in elderly patients. A 20-year experience. *Surgery.* 1998;123:335.)

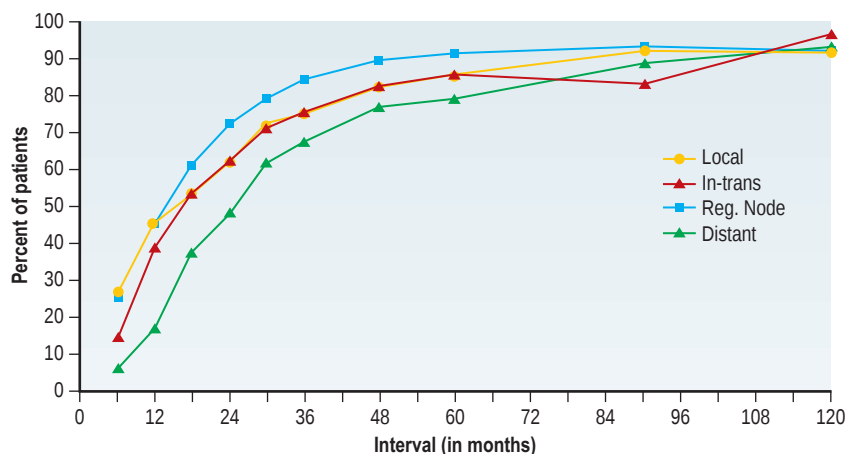


Fig. 29.35 Patterns and timing of recurrences for melanoma. The curve of the timing of local recurrence and in-transit metastases precedes that of lymph node recurrences and distant organ metastases. (From Fusi S, Ariyan S, Sternlicht A. Data on first recurrence after treatment for malignant melanoma in a large patient population. *Plast Reconstr Surg.* 1993;91:94.)

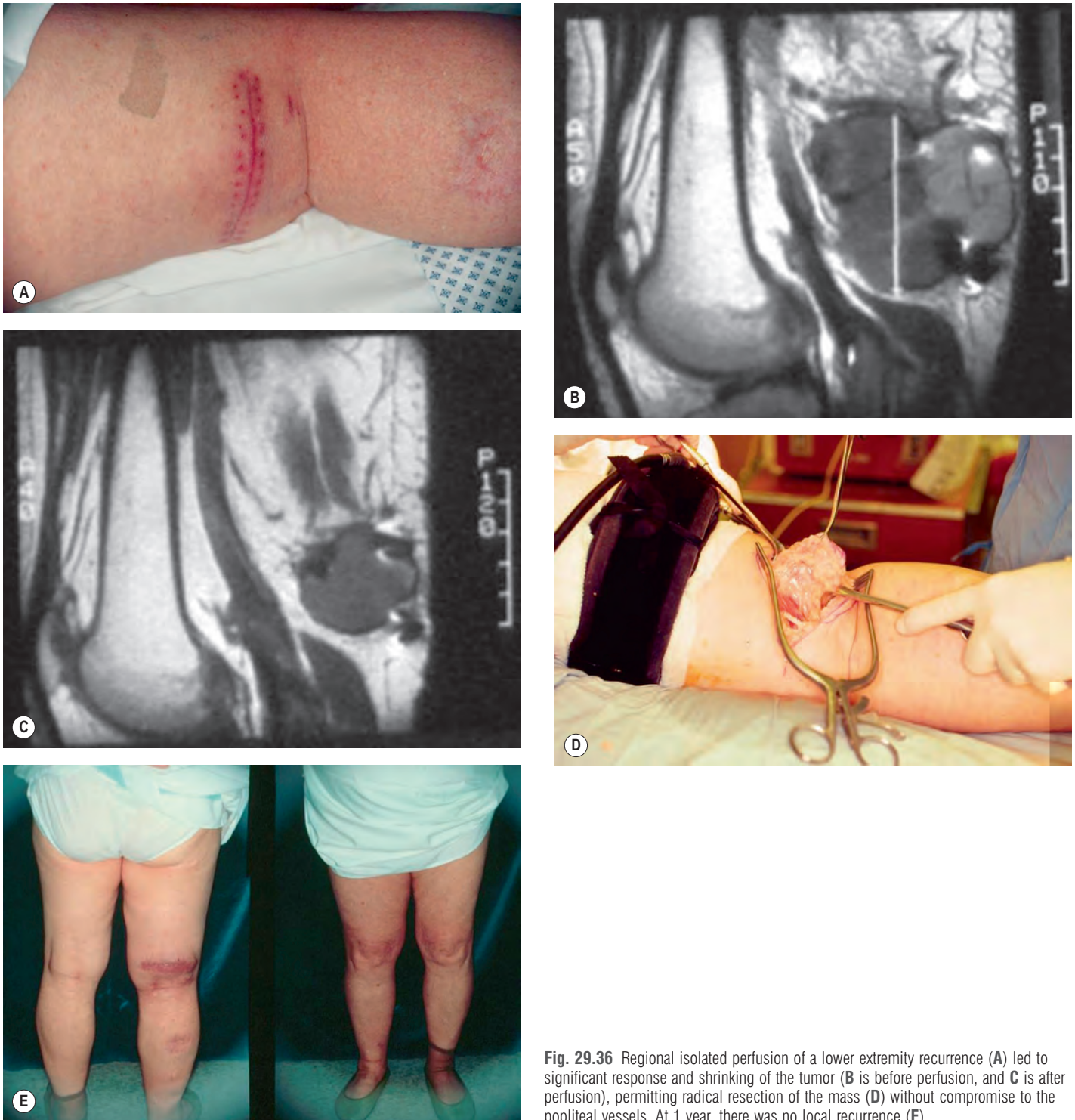


Fig. 29.36 Regional isolated perfusion of a lower extremity recurrence (A) led to significant response and shrinking of the tumor (B is before perfusion, and C is after perfusion), permitting radical resection of the mass (D) without compromise to the popliteal vessels. At 1 year, there was no local recurrence (E).

Treatment of metastatic melanoma

It is well-established that the prognosis of patients with metastatic melanoma is poor; those with liver, brain, or bone metastasis have a median survival of only 6 months. Brain metastases occur in more than 50% of patients with advanced melanoma.¹⁷⁰ The median survival of these patients is 4.4

months and the 5-year survival rate is approximately 3%.¹⁷¹ A number of systemic therapy options are available to treat patients with metastatic disease, including single-agent or multiple-agent chemotherapy, biochemotherapy, radiotherapy, or strategies using immune modulation. However, little consensus exists regarding standard therapy for patients with metastatic melanoma. From the surgical perspective, if the patient has metastatic disease localized to a single small focus

Table 29.10 Surgery for metastatic melanoma: outcome

Site of first recurrence	Incidence	5-year survival	Median survival
Skin, fat, lymph node	50%–60%	5%–40%	8–50 months
Lung	15%–35%	5%–30%	8–20 months
Gastrointestinal tract Small bowel (35%–65%) Colon (10%–15%) Stomach (5%)	2%–4%	Minority of patients Mostly palliative for symptomatic relief	10–20 months
Brain (at autopsy, 50%–80%)	8%–15%	Unexpected (5%) 80%–90% have symptomatic relief	6–8 months
Liver (rarely single metastasis)	5%	Anecdotal cases	–

(Modified from Allen PJ, Coit DG. The surgical management of metastatic melanoma. *Ann Surg Oncol*. 2002;9:762.)

in the lung, liver, or brain, it may be worthwhile to consider resection (Table 29.10). However, multiple recurrences cannot be treated by surgery and require consideration of systemic chemotherapy and/or radiation therapy. More recent advances have shown a very high response rate to gamma knife treatment of single or few metastases to brain.

Chemotherapeutic agents

Dacarbazine (DTIC) remains a standard of care in community practice, and has been used as a standard for comparing the efficacy of new regimens.^{124,172} Combination chemotherapeutic regimens that include other cytotoxic drugs, such as bis(2-chloroethyl)nitrosourea (BCNU), cisplatin, lomustine, and hydroxyurea, have been reported. The trials comparing DTIC alone or in combination with other agents have shown a significant though brief improvement in survival.¹⁷³ Dacarbazine and temozolomide have been shown to have similar response rates (approximately 10–20%) and survival,¹⁷⁴ with median response duration averaging approximately 3–4 months.^{173,174} Temozolomide can cross the blood–brain barrier, making it an attractive agent for treating melanoma, which has a propensity for metastasis to the brain.

Combination chemotherapy regimens such as CVD (dacarbazine plus cisplatin and vinblastine) or the Dartmouth regimen (dacarbazine, carmustine, cisplatin and tamoxifen) initially reported higher response rates,^{175,176} but subsequent clinical trials have not replicated these high response rates.¹⁷⁷ Paclitaxel, alone or in combination with carboplatin, may provide clinical benefit to some patients with metastatic

melanoma, but the duration of clinical benefit is short (2–7 months).^{178,179}

Tumor vaccines

The development of melanoma-specific tumor vaccines has been predicated on several clinical observations and lines of basic investigation that indicate that the immune system can eradicate melanoma cells. Although a comprehensive review of available vaccine strategies is beyond the scope of this chapter, some of the more encouraging studies are reviewed.

Ganglioside GM2, an antigen overexpressed by many melanoma cells, given in combination with bacille Calmette–Guérin (BCG) or other immune adjuvants, was developed by Haughton *et al.* at Memorial Sloan Kettering Cancer Center. Initial clinical trials suggested promising results,¹⁸⁰ however, further studies failed to show clinical benefit with this adjuvant treatment. Kirkwood *et al.*¹⁸¹ reported their experience comparing high-dose interferon alfa-2b and GM2 ganglioside vaccine for patients with resected melanoma, demonstrating the advantage of interferon. Additionally, a randomized Phase III trial (EORTC 18961) of adjuvant GM2-KLH21 in 1314 patients with stage II melanoma was closed early by the data monitoring committee because of inferior survival in the vaccine arm.¹⁸²

A polyvalent melanoma cell vaccine, developed at the John Wayne Cancer Center, was shown to be capable of inducing humoral and cell-mediated immune responses to melanoma-specific antigens.^{183,184} Nevertheless, this vaccine was found not to be beneficial in a clinical trial. Dr. Steven Rosenberg and co-investigators at the surgery branch of the National Cancer Institute have identified other cancer vaccines by using specific peptide antigens recognized by autologous tumor-specific T-cell clone reactivity.¹⁸⁵ Peptide vaccines are most often administered with cytokine or cellular immune adjuvants such as dendritic cells. DiFronzo *et al.*¹⁸⁶ demonstrated that enhanced humoral responses in patients treated with polyvalent vaccines resulted in limited but improved disease-free survival. It is difficult to advocate any of the current vaccine strategies over another, and we recommend that patients with high-risk melanoma be enrolled into prospective trials to test these therapeutic strategies.

Adoptive T-cell transfer

Rosenberg developed the concept of adoptive T-cell transfer, whereby tumor-infiltrating lymphocytes (TIL) isolated from an excised tumor can be expanded in the laboratory and infused back into the patient. The goal is for these cells to attack the tumor cells with an increased strength than the body would otherwise provide. A phase II trial of adoptive T-cell transfer in patients with stage IV melanoma demonstrated an objective response in 50% of patients.¹⁸⁷

Interleukin-2

Interleukin-2 (IL-2) was approved by the Food and Drug Administration (FDA) for treatment of metastatic melanoma in 1998. High-dose intravenous bolus IL-2 treatment resulted in overall objective response rates of about 17%.¹⁸⁸ In a highly selected patient population (n=270), IL-2 was able to induce durable complete responses (median response duration over 59 months) in approximately 6% of patients and partial

responses in 10% of patients with metastatic melanoma, albeit with high levels of toxicity.^{189,190} One study demonstrated increased response rate in metastatic melanoma when IL-2 was given with the 210M peptide vaccine (22%) compared to IL-2 (13%) alone.¹⁹¹

Biochemotherapy

Given the individual success of chemotherapeutic agents and the biologically active agents (IFN- α and IL-2), biochemotherapy regimens were developed. By combining conventional chemotherapeutic drugs with biologically active agents, investigators were able to demonstrate modest improvement in response rates of metastatic melanoma. In single institutional phase II trials, biochemotherapy (cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2) produced an overall response rate of 27–64% and a complete response rate of 15–21% in patients with metastatic melanoma.^{192–194} A report of a small phase III randomized trial comparing sequential biochemotherapy (dacarbazine, cisplatin, vinblastine with interleukin-2 and interferon alfa administered on a distinct schedule) with combined cisplatin, vinblastine and dacarbazine (CVD) showed response rates of 48% for the biochemotherapy regimen compared to 25% for CVD alone; median survival for patients treated with biochemotherapy was 11.9 months vs. 9.2 months for CVD.¹⁹⁵ In a phase III randomized intergroup trial (E3695), biochemotherapy (cisplatin, vinblastine, dacarbazine, interleukin-2 and interferon alfa-2b) produced a slightly higher response rate and progression free survival than CVD alone, but it was not associated with either improved quality of response or overall survival in patients with metastatic melanoma.¹⁹⁶ Biochemotherapy was substantially more toxic than CVD. Additional attempts to decrease toxicity of biochemotherapy by administering subcutaneous outpatient IL-2 did not show a substantial benefit of biochemotherapy versus chemotherapy alone.^{197–199} A meta-analysis demonstrated that although biochemotherapy seemed to improve overall response rates, there was no survival benefit for patients with metastatic melanoma.²⁰⁰

Given the overall poor performance of these agents, continued basic and translational research is warranted. Pre-emptive strategies are also being developed. Because a majority of patients with cutaneous melanoma have some identifiable risk factor (i.e., sun exposure), chemoprevention using carotenoids and inhibitors of cyclooxygenase-2 (COX-2), vascular endothelial growth factor (VEGF) receptor, and cytochrome P-450 are actively being investigated.²⁰¹ Outcomes of this work are much anticipated.

Immunotherapy-immune modulators

Despite many preclinical and clinical studies evaluating multiple cytokines, vaccines, antibodies, and other types of immune modulation, alone or in combination with chemotherapy, only IL-2 for metastatic disease and *interferon alfa* for surgical adjuvant treatment have demonstrated sufficient success to warrant approval by regulatory authorities.^{148,189} Nevertheless, there has been continued optimism that immune modulation can become an effective treatment for patients with melanoma driven largely by key advances in tumor immunobiology, including the potential to manipulate and

disrupt immune activation checkpoints and tumor defense mechanisms; newer approaches to antigen presentation for immune activation; refinements to procedures for antigen-specific T-cell expansion; gene transfer to alter lymphocyte specificity and function; and the potential for discovery of improved predictive biomarkers to select patients for individual treatments.²⁰²

Along these lines, Hodi *et al.* induced autoimmunity in patients with metastatic melanoma using ipilimumab, an antibody directed against the cytotoxic T-lymphocyte-associated antigen CTLA-4.²⁰³ CTLA-4 is an immune checkpoint molecule that down-regulates T-cell activation, and blocking this molecule is known to promote antitumor immunity.²⁰³ In their multicenter clinical trial, patients with metastatic melanoma were randomly assigned to receive either an anti-CTLA-4 agent (ipilimumab), a vaccine based on a melanoma antigen, or a combination of the anti-CTLA-4 agent and the vaccine. An improvement in overall survival, as well as an improvement in progression-free survival and best overall response rate, was seen in the patients who received anti-CTLA-4 therapy, as compared with the patients who received the vaccine only.²⁰³

In addition to CTLA-4, another extensively studied interaction is between programmed death-1 receptor (PD-1) on the surface of activated T cells with its ligand (PD-L1) on antigen-presenting cells or tumor cells. PD-1, like CTLA-4, is expressed on the surface of activated T cells, and when it binds PD-L1, the immune response is attenuated. The expression of PD-L1 on tumor cells is thought to play a role in decreased immune response in the tumor microenvironment, contributing to tumor growth and spread.

Of note, the side-effect profile of ipilimumab deserves mention, as 60% of patients suffered adverse events, mostly immune related. However, this randomized, controlled trial showed that there was a significant improvement in overall survival among melanoma patients treated with ipilimumab. It will likely prove useful in patients with metastatic melanoma whose disease progressed while receiving one or more previous therapies.

Phase I studies of PD-1 and PD-L1 inhibitors have demonstrated promising results in patients with metastatic melanoma.^{204,205} Randomized controlled trials evaluating survival benefits for PD-1 and PD-L1 inhibitors are currently being performed. Like ipilimumab, anti-PD-1/L1 medications have mostly immune-related adverse events. Early studies have been reported that are examining the combination of anti-CTLA-4 and anti-PD-1 medications. Treatment with concurrent nivolumab (anti-PD-1 antibody) and ipilimumab results in higher adverse event rates than administration of the drugs separately; however, most adverse events were reversible. An impressive response rate of 40% was seen in patients receiving the concurrent dosing versus 20% in those treated with a sequenced regimen.²⁰⁶ A subsequent update on this trial demonstrated an 82% survival rate at 1 year for the concurrent regimen and a 75% survival rate at 2 years.²⁰⁷ These results show improved response rates with the combination of multiple immunotherapy agents, and suggest that patients who experience disease progression on one agent may still benefit from the alternate agent. Given the results of these studies, as well as additional trials, nivolumab was approved by the FDA in December 2014 for the treatment of advanced melanoma after the failure of other treatments.²⁰⁸

Molecularly-targeted treatment of metastatic melanoma

Molecularly-targeted chemotherapy for metastatic melanoma has changed dramatically since 2010, with the advent of small inhibitor therapies, especially for melanomas with BRAF mutations. It was demonstrated in 2002 that approximately 50% of human melanomas harbor an activating mutation in BRAF, an upstream component of the mitogen-activated protein (MAP) kinase pathway; the mutation is a substitution of glutamic acid for valine (the V600E mutation).²⁰⁹ Melanoma cells containing the BRAF mutation are dependent on MAP kinase signaling for their growth and survival.²¹⁰ These findings suggested the possibility that melanoma may be amenable to targeted therapy.

There are three FDA-approved MAP kinase inhibitors used for the treatment of malignant melanoma: 2 BRAF inhibitors (BRAFi), vemurafenib and dabrafenib, and the first-in-class MEK inhibitor (MEKi), trametinib. Their approval was based on randomized, phase III trials in which each of the investigational agents was compared against dacarbazine for patients with unresectable BRAFV600E(K)-mutant MM.^{211–213} Responses were seen early during treatment, most responses were partial, and the development of secondary resistance was seen in the majority of patients.²¹⁴

It seems clear that melanomas can be categorized by specific molecular changes that drive their proliferation;²¹⁵ targeting the activated pathways in individual tumors may lead to tumor regression and possible cure. This type of personalized cancer therapy will likely play a prominent role in the care of patients with melanoma and other cancers in the coming decade.

Surveillance

Patients treated at the Yale Melanoma Unit are initially monitored closely (Table 29.11), with increasing intervals each year. The importance of dermatologic evaluation, photo documentation, and close follow-up cannot be overstated. Education of the patient for early self-detection of recurrences together with interval physician follow-up has been most successful in maintaining an effective monitoring program.²¹⁶ Patients are examined for local or in-transit metastases at varying intervals based on the stage of the melanoma at diagnosis (Table 29.12).

Tumor recurrences correlate with the thickness of the lesion. Between 60% and 70% of recurrences appear in the first 18 to 24 months after surgical treatment (see Table 29.8).¹⁶⁵ The earliest recurrences are to local or regional lymph nodes, followed by in-transit metastases; distant metastases appear last. Screening is typically by physical examination, liver-function

Table 29.11 Surveillance guidelines

Office visits and physical examination	
Stage 0	Yearly by dermatologist or primary care physician
Stage I	Every 6 months for 5 years
Stage II–IV	Every 3 months for 2 years Every 6 months for 3 years
Metastatic surveillance	
Lactate dehydrogenase level and complete blood cell count	At each visit, at least yearly
Chest radiograph	Every other visit, at least yearly
CT scan ± PET	With laboratory test or chest radiograph abnormality, physical findings, or symptoms

serology, and chest X-ray, which will detect most recurrences. Routine screening with CT of the head, chest, and abdomen is not recommended, unless clinical suspicion for metastases is high. Chest X-rays and liver serology, despite a relatively low yield,²¹⁷ are inexpensive and useful for establishment of baseline values. The utility of PET or PET-CT imaging for the surveillance of affected patients is still under investigation. Additionally, the prospect of using specific serum screening tools such as tyrosinase mRNA detected by RT-PCR is both clinically exciting and ethically challenging.²¹⁸

The National Cancer Institute recommends that most patients without a family history and no atypical nevi should have follow-up evaluations every 6 months for the first 2 years. Thereafter, yearly follow-up is appropriate. Those with a family history or atypical nevi are followed up every 3 months.²¹⁶

Summary

Melanoma remains a challenging and important clinical problem, with a rapidly rising yearly incidence. Wide local excision remains the primary treatment modality for primary disease. Sentinel lymph node biopsy is indicated for patients with clinically negative nodes and primary lesions with aggressive features, generally, thickness greater than 1 mm. If the SLN is positive, completion lymphadenectomy is indicated for control of regional disease. Unfortunately, the overall cure rates for advanced melanoma have not significantly improved during the past several decades because we are unable to treat the subclinical micrometastases that are present

Table 29.12 Protocol for follow-up surveillance

	Physical examination	Chest radiography	Liver function tests	Imaging
Stage I, T1	Semiannual × 2 yr, then annually	–	–	
Stage I–II, T2–4	Every 3 months × 3 yr, then semiannually	Annual	Annual	
Stage III (lymph nodes positive)	Every 3 months × 3 yr, then semiannually	Annual	Annual	Annual or as indicated

in systemic organs at the time of the treatment of the primary melanoma. Once these metastases become evident clinically, there is little chance of cure by further surgery, chemotherapy, radiation therapy, or combinations of these treatment modalities. Adjuvant trials with chemotherapy and biochemotherapy have not demonstrated uniform success for any meaningful period of time. Therefore, we cannot overemphasize the importance of clinical trials, and patients with advanced melanoma should be encouraged to enroll in clinical trials testing different adjuvant strategies whenever possible. Recent successes in controlling metastatic lesions with molecularly-targeted treatments hold promise for personalized treatments for genetic mutations in the future.



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Fig. 29.1 Autopsy findings of patient with melanoma of right ankle spreading in a centripetal manner to right groin and remainder of body while sparing the left leg. (Redrawn from Handley WS. The pathology of melanotic growths in relation to their operative treatment. Lecture I. *Lancet*. 1907;1:927.)

Fig. 29.2 Handley recommended removal of melanoma (a) together with 1 inch (f) of skin (b) and 2 inches (g) of underlying subcutaneous fat (c), muscle fascia (d), and muscle (e). h, skin incision. (Redrawn from Handley WS. The pathology of melanotic growths in relation to their operative treatment. Lecture I. *Lancet*. 1907;1:927.)



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Implants and biomaterials

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SYNOPSIS

- What is a biomaterial? In order to discuss biomaterials, we must first define this term.
- There are many definitions of biomaterials but a widely used one from the National Institutes of Health defines a biomaterial as “any substance (other than a drug) or combination of substances synthetic or natural in origin, which can be used for any period of time, as a whole or part of a system which treats, augments, or replaces tissue, organ, or function of the body”.¹
- With the advent of tissue engineering and regenerative medicine in recent years, the definition has broadened to include “any material used in a medical device intended to interact with biological systems”, allowing for structures and combination devices that actively interact with the body to be included in the field.²
- Biomaterials can be synthetic (i.e., those made by humans) or biological (i.e., those produced by a biological system).
- Further classifications based on development stage or material characteristics are also common but are beyond the scope of this chapter.

Access the Historical Perspective section and [Box 30.1](#) online at

<http://www.expertconsult.com>

For the purpose of this chapter, biomaterials will be divided into the following general categories: metals, polymers, ceramics, glues, skin substitutes, and bioprosthetics.

Metals

In order to achieve the mechanical and biophysical properties desired for applications in medicine, combinations of metals, called alloys, have been developed. These alloys are designed to be inert and withstand the corrosive environment found

within the human body. In general, these alloys have mechanical properties that exceed the properties of the natural tissue they are supporting because, unlike natural tissues, they are unable to recover from deformation.

Stainless steel

Stainless steel has been used as a biological implant since the 1920s.⁶ Stainless steel was designed to prevent corrosion and consists of over 10 individual compounds which provide it with the desired chemical and mechanical properties. The stainless steels used in medical applications are iron-chromium-nickel alloys with at least 17% chromium ([Table 30.1](#)). The chromium creates a protective surface, which contributes to the alloy's anticorrosive properties. The most commonly used stainless steel alloy in medical applications is “316L” which, in addition to the chromium composition, has a low carbon content to prevent carbide formation, and a high nickel content to increase the strength and hardness of the alloy. Stainless steel has a relatively high tensile strength but is easily deformed (bent). While this is useful in some applications, such as the application of arch bars for maxillomandibular fixation, overall these mechanical properties are less desirable than other currently available materials such as cobalt-chromium and titanium. In addition, stainless steel can leach metallic ions into the surrounding tissues, causing a severe inflammatory reaction and pain, which may require surgical removal of the implants in some patients. Stainless steel is currently used in surgical wire and in arch bars. Historically rigid fixation systems utilized stainless steel but other alloys have replaced stainless steel in this application.

Cobalt-chromium

Historically, cobalt-chromium alloys have been one of the most significant biomaterials used in humans. Vitallium, a cobalt-chromium-molybdenum (Co-Cr-Mo) alloy (ASTM 75), was first described in 1932 to address some of the problems experienced with stainless steel. These alloys replace the iron

Historical perspective

The development of biomaterials has exploded over the past 50 years. In fact, prior to World War II, the term “biomaterials” did not exist. Although there have been reports of biomaterials being used, in the form of sutures, 32 000 years ago,^{2,3} the vast majority of biomaterials have been developed in the last 60 years. The modern era of medical implants might be attributed to a British ophthalmologist, Harold Ridley, in the late 1940s. He noticed that shards of canopy plastic that had been unintentionally implanted in the eyes of Spitfire fighter pilots who had been shot at by enemy machine guns seemed to heal without any adverse reaction. He concluded that the plastic used to make the Spitfire canopy, poly(methyl-methacrylate), might be used to make implant lenses for patients with cataracts. In 1949 he implanted the first artificial lens into a human. This observation and innovation were the precursors to the modern intraocular lenses that are now used over 10 million times per year for patients with cataracts.²

Around the same time, several independent groups of surgeons and engineers developed biomaterial-based implants such as vascular grafts, hip replacements, and heart valves. These innovators defined the foundations of biomaterial science in an era before principles for medical materials were established. By the 1950s, as surgeons, engineers, and scientists continued to create these new implant materials, it

BOX 30.1 Properties of an ideal implant

- Minimal foreign-body reaction
- Elastic or supple
- Can be tailored easily
- Good tissue incorporation
- Allows collagen ingrowth
- Promotes permanent tissue repair
- Good tensile strength
- Tolerates infected environment
- Minimal wound complications

(Modified from Cumberland VH. A preliminary report on the use of prefabricated nylon weave in the repair of ventral hernia. *Med J Aust.* 1952;1:143–144; and Scales JT. Materials for hernia repair. *Proc R Soc Med.* 1953;46:647–652.)

became clear that there were certain properties that an ideal implant would impart. Cumberland⁴ and Scales⁵ described the properties of an ideal implant (Box 30.1).

Remarkably, although these criteria were published about 60 years ago, they are still the fundamental properties that all modern biomaterials attempt to achieve.

Table 30.1 Composition of common metal alloys

Element	Stainless steel (ASTM F138)*	Co-Cr (ASTM F90)†	Titanium (ASTM F136)‡
	Weight %	Weight %	Weight %
Chromium	16–18	27–30	–
Nickel	10–14	2.5 max	–
Molybdenum	2–3	5–7	–
Carbon	0.03 max	0.35 max	0.08 max
Iron	Balance	0.75 max	0.25 max
Manganese	2.00 max	1.00 max	–
Phosphorus	0.045 max	–	–
Sulfur	0.03 max	–	–
Silicon	1.00 max	1.00 max	–
Nitrogen	0.10 max	–	–
Cobalt	–	Balance	–
Oxygen	–	–	0.013 max
Aluminum	–	–	5.5–6.5
Vanadium	–	–	3.5–4.5
Titanium	–	–	Balance

*ASTM. Standard specification for wrought 18chromium-14nickel-2.5molybdenum stainless steel bar and wire for surgical implants (UNS S31673). West Conshohocken, PA: ASTM International; 2008.

†ASTM. Standard specification for wrought cobalt-20chromium-15tungsten-10nickel alloy for surgical implant applications (UNS R30605). West Conshohocken, PA: ASTM International; 2009.

‡ASTM. Standard specification for wrought titanium-6 aluminum-4 vanadium ELI (extra low interstitial) alloy for surgical implant applications (UNS R56401). West Conshohocken, PA: ASTM International; 2008.

(Adapted from Holmes RE. Alloplastic materials. In: McCarthy JG, ed. *Plastic Surgery*. New York: WB Saunders; 1990:698–731.)

with cobalt (~60% of the composition), increase the chromium to 25–30% for additional corrosion resistance, and contain 5–7% molybdenum for additional strength (see Table 30.1). Co-Cr-Mo alloy was used in some of the early craniofacial miniplates and screws and helped to revolutionize that field. The major disadvantage of Co-Cr-Mo alloys is the scatter artifact on computed tomography (CT) imaging. Because of this, and several other benefits, titanium has essentially replaced Co-Cr-Mo alloys in most biomedical applications.⁷ However, it is still used in dental applications.

Titanium

Titanium alloys were introduced into medical applications in the early 1980s.^{6,8} Since that time titanium has almost entirely replaced the other alloys in medical applications. This is because the titanium alloys are stronger, lighter, have higher resistance to corrosion, and generally cause less inflammation. Titanium also has less stress shielding (localized osteopenia secondary to the implant protecting the bone from normal loading) than other metal implants because they have less stiffness. Titanium alloys have less than 0.5% iron in them (see Table 30.1), which provides them with two additional beneficial properties: they do not set off metal detectors, and they do not create a significant artifact on CT or magnetic resonance imaging studies. Finally, titanium can form chemical bonds with the surrounding mineralized bone without the typical fibrous tissue forming between the implant and bone. This unique characteristic allows titanium to be used to create osteointegrated implants. In many cases pure titanium rather

than an alloy is used for medical implants. Plastic surgery applications of titanium include plates and screws for rigid fixation of bone and mesh for use in applications such as orbital wall reconstruction (Fig. 30.1).

Gold

Although gold is chemically inert, in its pure form it has poor mechanical properties. Thus, when some strength is needed (for example, in dental fillings), a gold alloy is used. For applications such as eyelid weights in patients with lagophthalmos,⁹ where strength is less of an issue, 24-carat gold alloy (99.9% w/w purity) is commonly used to insure chemical inertness.

Platinum

Like gold, platinum is an inert metal and is the material of choice for patients with gold sensitivity who are in need of an eyelid implant for lagophthalmos. Platinum is denser than gold, thus the eyelid implants have a lower profile and are less noticeable than gold implants.

Some formulations containing platinum have been shown to be immunogenic and thus have raised concerns over long-term exposure. Because the Centers for Disease Control state that short-term exposure to platinum salts may cause irritation of the eyes, nose, and throat and long-term exposure may cause both respiratory and skin allergies, the current Occupational Safety and Health Administration standard for soluble platinum salts is 2 mcg/m³ of air averaged over 8 hours.



Fig. 30.1 Titanium plates for midface reconstruction. **(A)** Various 2.0-mm plates and screws. The screws are 7, 5, and 3 mm in length (left to right). **(B)** Four-hole plates and screws for the 1.0-, 1.5-, 2.0-, and 2.3-mm plating systems. **(C)** A 1.0-, 1.5-, and 2.0-mm “L” plate. The screws are all 5 mm in length. Note that, by convention, the size of the plates is based upon the screw diameter.

Platinum is also used as a catalyst in the formation of some polymers. Platinum black, a fine powder (1 nm–1 μ m) form of platinum, is used in many of these reactions.¹⁰ Platinum black catalyzes the addition of hydrogen to unsaturated organic compounds and is used in the production of silicone gel breast implants (see below).

Platinum complexes have also been used as chemotherapy and show good activity against some tumors. Cisplatin, the best-known platinum chemotherapeutic agent, has activity against multiple types of cancer. However, it has some significant side effects, including cumulative irreversible kidney damage and deafness.^{11,12}

Polymers

Polymers are molecules composed of repeating subunits. They are typically defined as a backbone series of molecules with side chains that are covalently bound to the backbone molecules. The physical properties of the polymer are defined by the structure of the monomer, the number of monomer units in the polymer chain, and the degree of cross-linking (the amount of bonding between two polymer chains). As

polymer chains are cross-linked, the ability for them to move independently is decreased. For example, a polymer with freely flowing chains might exist as a liquid and, as the amount of cross-linking is increased, it can become a “gel” or “solid”.

Silicone

Silicone is probably the most maligned and misunderstood biomaterial used in medicine today. This is likely due to the controversy revolving around the use of silicone in breast implants. Silicone gel-filled breast implants were first introduced in the US in 1962 and consisted of two shells made of thick, smooth-walled silicone elastomer, filled with a viscous silicone gel material (dimethylsiloxane) and glued together. Multiple variations and modifications to the shell and gel were made over the years in an attempt to improve the outcomes of breast augmentation and reduce the associated complications. In 1988, the US Food and Drug Administration (FDA), out of concerns from reports of implant failure and allegations of resultant complications and illness, relabeled breast implants as class III medical devices, and called for data from manufacturers showing the safety and effectiveness of these devices.^{13,14}

In 1992, the FDA claimed that there was “inadequate information to demonstrate that breast implants were safe and effective” and placed a moratorium on silicone gel breast implants for cosmetic purposes but allowed their continued use for reconstruction after mastectomy, correction of congenital deformities, or replacement of ruptured silicone gel-filled implants due to medical or surgical reasons. In order to address this concern, the Department of Health and Human Services appointed the Institute of Medicine of the National Academy of Science (IOM) to begin one of the most extensive research studies in medical history. Their charge was to examine potential complications during or after silicone-based breast implant surgeries. In 1999, after reviewing years of evidence and research concerning silicone gel-filled breast implants, the IOM released a comprehensive report on both saline-filled and silicone gel-filled breast implants entitled *Safety of Silicone Breast Implants*.¹⁵ The IOM found that “evidence suggests diseases or conditions such as connective tissue diseases, cancer, neurological diseases or other systemic complaints or conditions are no more common in women with breast implants than in women without implants”. Most individual studies and all systematic review studies have also subsequently failed to find a link between silicone breast implants and disease.^{13,14}

In 2006, the ban imposed by the FDA was lifted and restrictions on the use of silicone gel-filled breast implants produced by the two manufacturers for breast reconstruction and for cosmetic breast augmentation ended. The FDA approval required a complete 10-year study on women who have already received the implants and a 10-year study on the safety of the devices in 40 000 women. It was also mandated that patients be given brochures explaining the risks.^{13,14}

So what is silicone? It is important to understand this question in light of the history of breast implants. Silicone is a family of polymers consisting of alternating silicon (Si) and oxygen (O) molecules. Table 30.2 shows the nomenclature of silicone. Siloxane, the basic repeating unit of silicone, consists of silicon, oxygen, and a saturated hydrocarbon (alkane) side group. Poly-dimethylsiloxane (PDMS) $[(CH_3)_2SiO]_n$ is the polymer used in most medical applications. PDMS is a very pure polymer that consists of the silicone backbone (silicon and oxygen) with two methyl side chains. It is one of the most inert biomaterials available for use in medical devices. Altering the length and molecular weight of the PDMS changes the mechanical properties and behavior of the silicone gel. PDMS molecules with less than 30 monomers are defined as low-molecular-weight formulations and have a viscosity similar to baby oil. High-molecular-weight formulations contain more than 3000 monomers and are solids. Controlling the degree of cross-linking, changing additives, and adjusting the curing process can also modify the mechanical properties of silicone. For example, the silicone gel found in breast implants is cured in a hydrosilation reaction where some of the methyl side chains (CH_3) are replaced by vinyl side chains ($CH=CH_2$) that then allow the silicone chains to cross-link with each other. This reaction is catalyzed by platinum and some residual platinum can be found in silicone gel breast implants. The silicone shell on breast implants is made of fully polymerized silicone with an amorphous (noncrystalline) silica filler added for strength (Fig. 30.2).

Other plastic surgery applications of silicone include facial implants for malar, nasal, and chin reconstruction or

Table 30.2 Silicone nomenclature

Term	Chemical formula	Description
Silicon	Si	Most abundant element on earth Does not occur naturally in its metallic state
Silica	SiO_2	Sand, marble, or quartz
Silicate	Na_2SiO_3	In one form, used as a desiccant (e.g., in anesthesia machines)
Siloxane	R_2SiO	Monomer of silicon and oxygen
Silicone	$[R_2SiO]_n$	Polymers of silicon and oxygen
Poly-dimethylsiloxane	$[(CH_3)_2SiO]_n$	The building block for most medical-grade silicone products, including breast implants

(Adapted from Miller MJ, Ogunleye OT. Biomaterials. In: Guyuron B, Eriksson E, Persing JA, et al., eds. *Plastic Surgery Indications and Practice*. New York: Saunders Elsevier; 2009:57–66.)

augmentation, and orbital floor reconstruction. Hand surgeons use silicone implants for arthroplasty, flexor tendon replacement, and bone block spacers. Silicone is beneficial in these applications because it is relatively inert, malleable, and deformable. Low-molecular-weight silicone was used in the past as an injectable soft-tissue filler. However, severe tissue reaction and migration of the silicone have led many physicians to avoid this application.

Silicone is probably the most studied implantable material available today. After over 35 well-conducted studies from many countries, there is no conclusive evidence that this material causes disease. Furthermore, medical-grade silicone is ubiquitous, being found in more than 1000 medical products as either a component or as a residuum from the manufacturing process. For example, every disposable needle and syringe,



Fig. 30.2 A silicone gel-filled breast implant (Mentor).

as well as intravenous tubing, is lubricated with silicone. Medications in stoppered vials contain residual silicone from its use in the manufacturing process. Silicone elastomers, in their solid form, are used for pacemaker coatings, tubing, prosthetic joints, hydrocephalus shunts, and various facial and penile implants. Like breast implants, some testicular and chin implants are made of a silicone gel in a silicone envelope.

Silicones are also found in some medications. If a medication contains an ingredient with the name “methicone” (e.g., simethicone), this is a silicone that has been modified for human consumption. Silicones are also used in household items such as lipstick, suntan/hand lotion, hairspray, processed foods, and chewing gum. Medical-grade silicones invoke a nonspecific foreign-body response, resulting in typical macrophage invasion, giant cell formation, and eventual scarring.¹⁶

Extensive investigations by several prestigious scientific bodies (e.g., the IOM,^{17,18} and the UK Department of Health¹⁹) have failed to show that systemic illness is definitively attributed to silicones. However, in January of 2011, the FDA, based upon a series of case reports which followed the sentinel case reported in 1997,²⁰ issued a safety communication stating, “women with breast implants may have a very small but increased risk of developing anaplastic large cell lymphoma (ALCL) in the scar capsule adjacent to the implant”.^{21,22} At the time of the communication, the FDA was aware of approximately 60 cases of breast implant patients who had developed ALCL out of the approximately 5–10 million women who had received breast implants worldwide. Since then over 200 women worldwide have been diagnosed with breast implant-associated ALCL (BI-ALCL). The exact cause and mechanism of BI-ALCL is unknown but is not limited to women with silicone-filled implants as women with saline filled implants have also developed the disease.^{23,24} For more details about BI-ALCL the reader is referred to Volume 5, Chapter 12.

The next progression in silicone gel breast implants was the approval by the FDA of cohesive gel implants (commonly referred to as “gummy-bear” implants). All three breast implant manufacturing companies have received approval for their cohesive gel implants, Sientra (Santa Barbara, CA) in March 2012; Allergan (Irvine, CA) in February 2013; and Mentor (Irvine, CA) in June 2013.²⁵

Polytetrafluoroethylene

Polytetrafluoroethylene (PTFE), also known as Teflon, was accidentally invented by Roy Plunkett in 1938 while he was trying to develop a refrigerant.²⁶ It consists of a carbon backbone with fluorine side chains. Expanded PTFE (ePTFE or Gore-Tex) was created by Bob Gore in 1969 when he rapidly stretched PTFE. It is very stable chemically, cannot be cross-linked (which makes it flexible), and has a nonadherent surface. When made with a pore size of 10–30 μm it will allow some limited tissue ingrowth. It has been used for a wide variety of applications, from hiking boots to coatings on frying pans. Within the medical field it is used for vascular grafts, mesh for abdominal wall reconstruction, and implants for facial augmentation.²⁷ The nonadhesive properties of ePTFE have been employed in surgical meshes used for hernia repair to reduce repair site adhesion. However, there are

significant limitations of ePTFE mesh used for hernia repair, including infection often requiring explantation and limited incorporation strength to the surrounding fascial edge compound to macroporous meshes such as polypropylene.

Polyester

Polyester contains an ester functional group in its main chain. Mersilene is a polyester fiber mesh knitted product for use in herniorrhaphy. Polyester mesh is softer and more hydrophilic than polypropylene, and in animal studies has shown better tissue ingrowth. Dacron is another form of polyester that has been used for vascular grafts.

Polypropylene

Polypropylene, or polypropylene, has a carbon backbone and side chains of hydrogen and methyl groups. It has been used in hernia and pelvic organ prolapse repair and is rarely rejected. However, polypropylene mesh can erode through the soft tissues over time. Therefore, the FDA has issued warnings on the use of polypropylene mesh in pelvic organ prolapse, specifically when in close proximity to the vaginal wall secondary to the number of mesh erosions reported by patients over the past few years.²⁸ It is also used as suture material because of its strength and low foreign-body reaction within the body. Knitted polypropylene surgical meshes are commonly used for hernia repair owing to a high ultimate tensile strength of the mesh and strong fibrovascular incorporation into the fascial defect edge. Direct placement over abdominal viscera can cause dense adhesions, fistula, and erosion. Reoperation through a polypropylene mesh hernia repair is often challenging due to this generalized fibrotic scarring to adjacent intraperitoneal viscera.

Polyethylene

Polyethylene consists of a carbon backbone with hydrogen side chains (ethylene). A high-density porous form of polyethylene (Medpor) is used for facial implants (Fig. 30.3). The



Fig. 30.3 Medpor (high-density porous form of polyethylene) implants used in facial augmentation.

porosity allows for tissue and vascular ingrowth. It can also be carved to customize the implant for individual patients. The implants are firmer and stiffer than the ePTFE implants and, because of the size of the pores, are more difficult to place because the soft tissues adhere to it more readily. In addition, the soft-tissue ingrowth makes the implant more difficult to remove. Porous polyethylene alone or with titanium mesh embedded within it is available for reconstruction of the orbital floor. One of the disadvantages of the polyethylene alone for orbital floor reconstruction is that the implant does not show up well on CT, making it difficult to diagnose a malpositioned implant.

Biodegradable polymers

Biodegradable polymers were developed to try to overcome some of the disadvantages associated with permanent implants. Most biodegradation begins through a chemical reaction such as hydrolysis or oxidation and involves some sort of biological process (e.g., enzymatic or cellular process) to eliminate the material completely. In addition to the requirement that the material itself must be biocompatible, all of the breakdown products of the material must be biocompatible as well.²⁹

Although there are a multitude of materials that will degrade *in vivo*, there are only a few that are clinically relevant as biodegradable polymers. Most of these are α -hydroxy acids, specifically poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and combinations, or copolymers, of these individual polymers know as poly(lactic-co-glycolic acid) (PLGA). These polymers degrade through hydrolysis, ending in lactic or glycolic acid, a common byproduct of normal biochemical pathways.

Most surgeons are familiar with this polymer as it is the polymer used to make Vicryl (polyglactin 910; Ethicon, Somerville, NJ). These polymers have also been used to create biodegradable mesh for use in abdominal wall reconstruction and plating systems for craniofacial or hand applications.

Altering the ratios of lactic to glycolic acid or adding carbon fibers or other polymers can modify the rate of degradation. In general, increasing the concentration of lactic acid decreases the rate of degradation (i.e., the polymer lasts longer). In the past 15 years manufacturers have used these polymers to develop biodegradable plates and screws for craniofacial and hand applications. Each manufacturer has modified the ratio of lactic and glycolic acid as well as the specific manufacturing protocol to optimize the degradation rate and strength of the polymer. For example, LactoSorb (Biomet, Warsaw, IN) consists of 82% PLA and 18% PGA while Resorb X (KLS Martin, Jacksonville, FL; used in SonicWeld) is 100% poly D,L-lactic acid (PDLLA). At implantation, their strength is equal to that of titanium plating and decreases with time. Typically the structural integrity is preserved for the first 8 weeks to allow for bony healing to occur.

Vicryl knitted meshes are used as a temporary abdominofascial closure in complex abdominal wall reconstruction, particularly in a contaminated wound. The mesh helps contain the viscera initially and subsequently resolves, creating an iatrogenic hernia that is repaired in a delayed stage.

Ceramics

People have been using ceramic materials for thousands of years. However, medical applications of ceramics were not developed until the 1960s. Of the many ceramics available, only a few have been found to be suitable for implantation in humans. Ceramics have a crystalline structure and are made up of inorganic, nonmetallic molecules whose individual electrons are strongly bound to each individual atom (called heteropolar bonding; in contrast, homopolar bonding, seen in metals, allows the electrons to flow freely between atoms). The manufacturing of ceramic materials is achieved through a process called sintering, which requires the material to be fused together under high pressure and temperature. Ceramics have appealing physical properties for biomedical use, including decreased foreign-body response, resisting bacterial colonization, a high compressive strength, and tissue ingrowth into porous materials (100 μm pore size for bone and 30 μm pore size for soft tissue). However, their benefits are overshadowed by their weaknesses; namely they are brittle and fracture easily under tensile, torsional, or bending loads. Their main uses in plastic surgery are for bone augmentation and replacement.

Calcium phosphates are the most common ceramics used in plastic surgery. In addition, calcium phosphates have been shown in the laboratory to be both osteoinductive and osteoconductive, but this has not been demonstrated in the clinical setting.

Calcium phosphates come in two formulations for medical use: hydroxyapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$) and tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$). Tricalcium phosphate has a faster rate of resorption and replacement by bone when compared to hydroxyapatite. They are available as granules for injection, blocks, both solid and porous, and the hydroxyapatite is also available as a cement paste. These implants are commonly used to reconstruct nonload-bearing bones of the face and cranium. The cement paste is beneficial in select cases, such as cranioplasty, because it is malleable and can be molded during the case.

Adhesives and glues

The first fibrin tissue adhesive was described in 1944 and was used to aid in the adherence of skin grafts to the recipient tissue bed. The first commercially manufactured fibrin sealant became available in 1978. Cyanoacrylate was synthesized in 1949 but this early product created a severe foreign-body reaction. Through chemical modifications to molecule, engineers were able to decrease the foreign-body reaction and create a clinically relevant product. There are several tissue adhesives available for clinical use. Most commonly, these adhesives are used to seal two tissues together or to provide hemostasis. Many of the adhesives possess both properties. Ideally, tissue adhesives should possess five characteristics (Box 30.2). Several classes of tissue adhesive are available and each will be discussed in the next sections.³⁰

Platelet gels

Platelet gels are derived from platelet-rich plasma (PRP). The starting material is 70 mL of whole blood that undergoes

BOX 30.2 Characteristics of the ideal tissue adhesive

- Must be safe (i.e., no allergic response, disease transmission)
- Must eliminate potential spaces
- Must be easy to use
- Must be cost-effective
- Must have a clinical benefit

centrifugation. The platelet layer, which also contains native fibrinogen, is then combined with bovine thrombin, resulting in a gel adhesive. This product is good for individuals who do not want to use the commercially available fibrin sealant. It is also less expensive to manufacture (once the initial equipment is accounted for) than the commercially produced fibrin sealants. There are, however, some drawbacks to this product. The concentration of fibrinogen in PRP is significantly lower than in the commercially available fibrin sealants. Thus, the PRP is a less effective adhesive. In addition, the tensile strength and hemostatic capabilities of PRP are also lower than the commercially available products. The clinical applications of this product include brow lift, facelift, abdominoplasty, the latissimus dorsi donor site, and deep inferior epigastric perforator/transverse rectus abdominis myocutaneous flap donor sites, where there is a large surface area that the surgeon would like to adhere together. Spray or mist applicators provide the best delivery method.

Fibrin tissue adhesives

Fibrin sealants were the first FDA-approved tissue adhesives and consist of two parts: fibrinogen and thrombin. A small amount of factor XIII and calcium is included to catalyze the reaction and form polymerized fibrin. Screened donors provide pooled human plasma as the source of the two ingredients. The commercially available product also contains an antifibrinolytic to decrease degradation and bovine-derived aprotinin, which acts as a stabilizer. In order to prevent disease transmission, the products undergo heat pasteurization and ultrafiltration.

The product must be refrigerated and requires approximately 20 minutes to prepare. The two bottles need to be placed in a special warmer for several minutes. Once heated, the components are drawn up into individual syringes. The dual syringe delivery system is designed to mix the two ingredients immediately before they are applied. There are multiple delivery mechanisms available. The simplest delivery system is a straight blunt-tipped needle. There are also sprayer/mister applicators and applicators for endoscopic use. The misters provide the maximal mixing of the two components and produce the thinnest layer of polymerized fibrin to the wound, which has been shown to have the strongest adhesive properties.³¹

The strength of the fibrin glue is directly proportional to the concentration of fibrinogen in the mixture while the rate of polymerization is regulated by the concentration of the thrombin. Thus, in applications where the tissues need to be manipulated (e.g., a large flap), a lower concentration of thrombin should be used. Plastic surgery applications for fibrin sealants are similar to the indications for PRP described

above. Fibrin sealants have also been used successfully to treat chronic seromas with percutaneous injection.³²

Cyanoacrylate

The original cyanoacrylates were butyl-cyanoacrylate. The butyl-cyanoacrylate is a short chain with rapid breakdown, which resulted in many wounds dehiscing. In addition, the breakdown products (formaldehyde and cyanoacetate) can cause a severe inflammatory reaction if butyl-cyanoacrylate penetrates the skin. In order to address these issues, octyl-cyanoacrylates were developed. They have longer side chains, creating a stronger and longer-lasting polymer. The polymerization begins when the 2-octyl-cyanoacrylate is exposed to moisture (there is enough moisture in the air to allow polymerization to occur). Applications in plastic surgery are limited to skin closure. Because the superficial layer of the skin, where the product is applied, will not have any sutures to hold it together, it is important to make sure the deep layers are well approximated and provide a tension-free abutment of the two sides. Studies that have been done comparing traditional suturing to using octyl-2-cyanoacrylate showed that the outcomes were equivalent.³³

Skin substitutes

Over the past 25 years, bioengineered skin substitutes have become a mainstream therapy for wound management.³⁴ Originally designed to replace skin grafts for patients with severe burns, their use has broadened to include the treatment of chronic venous and chronic diabetic ulcers. As these technologies continue to advance, their application will broaden even further (Box 30.3).

Although the ideal skin substitute does not exist, engineers and scientists have developed, and continue to refine, several very useful products. The engineering of cultured skin substitutes has been developed on the premise that three important components are required for their formation: (1) a cell source; (2) a “tissue differentiation-inducing” substance; and (3) a matrix.³⁵ A variety of cells, mediators, and polymers have been tested in various combinations to engineer cultured skin substitutes. We review the most common of these below and compare them in Table 30.3.

Integra

Integra (Integra LifeSciences, Plainsboro, NJ) is a bilayer skin substitute. The “dermal” (lower) layer is a bovine collagen

BOX 30.3 Characteristics of an ideal skin substitute

- Adhere to the wound bed rapidly
- Recapitulate the physiologic and mechanical properties of normal skin
- Be inexpensive
- Avoid immune rejection by the host
- Be highly effective in accelerating tissue regeneration and wound repair.

Table 30.3 Comparison of commercially available skin substitutes

Product	Company	Tissue of origin	Layers	Uses
Integra	Integra Life Sciences Plainsboro, NJ	Synthetic	1. Silicone 2. Collagen and GAG matrix	Deep- or full-thickness soft-tissue defects for coverage Requires skin graft
Epicel	Vericel Corp. Cambridge, MA	Autogenous	Cultured autogenous keratinocytes	Deep partial- and full-thickness burns >30% TBSA
Dermagraft	Organogenesis Canton, MA	Allogeneic dermis	Vicryl seeded with neonatal fibroblasts	Chronic wounds Full-thickness burns with STSG
Apligraf	Organogenesis Canton, MA	Allogeneic composite	1. Neonatal keratinocytes 2. Collagen seeded with neonatal fibroblasts	Chronic wounds Excision sites Used with STSG to improve function/cosmesis
AlloDerm	LifeCell Branchburg, NJ	Allogeneic dermis	Acellular dermis	Deep partial- and full- thickness burns Soft-tissue replacement Suspensory materials Interpositional grafts Tissue patches

GAG, glycosaminoglycan; STSG, split-thickness skin graft; TBSA, total body surface area.

(Adapted from Shores JT, Gabriel A, Gupta S. Skin substitutes and alternatives: a review. *Adv Skin Wound Care*. 2007;20:493–508; quiz 509–510.)

base with glycosaminoglycan chondroitin-6-sulfate while the upper layer is a silicone sheet that acts as a temporary epidermis.³⁶ As the wound heals the dermal layer is replaced with the patient's own cells.³⁷ A thin split-thickness skin graft is then applied on to the neodermis. Integra is indicated for the management of complex wounds such as partial- or full-thickness burns, and multiple types of ulcer. Several studies have evaluated the efficacy of Integra and have compared Integra with autograft, allograft, xenograft or Biobrane. Biobrane (Smith & Nephew, Largo, FL) is a biosynthetic dressing constructed of a silicone film with a collagen-bound nylon fabric partially embedded into the film. These studies showed that Integra has a higher rate of infection than the other tested product with regard to wound infection and graft take. However, Integra appeared to be better than autograft, allograft, or xenograft in terms of wound-healing time. Integra is also used in complex wounds to which a skin graft would not adhere.^{36,38,39} The neodermis attaches to the underlying bed, vascularizes over 10–14 days, and then provides a surface for a split-thickness skin graft to adhere to.

Epicel (cultured epidermal autografts)

Epicel (Vericel Corp., Cambridge, MA) is a cultured epidermal autograft grown from the patient's own keratinocytes. A small skin biopsy is harvested from the patient and sent to the company for processing. The keratinocytes are grown in a co-culture using proliferation-arrested, 3T3 murine fibroblast feeder cells. Once the keratinocytes are 2–8 cell layers thick the autograft is returned to the patient for grafting. The graft is attached to petrolatum gauze backing with stainless steel surgical clips and measures approximately 50 cm².

Epicel is indicated for patients who have either deep dermal or full-thickness burns involving a total body surface area of greater than or equal to 30%. It can be used in conjunction with split-thickness skin grafts, or alone in patients for whom split-thickness skin grafts may not be an option due to the severity and extent of their burns. Epithelial cells have been

combined with Integra to regenerate skin and oral mucosa successfully in animal models. This has been performed with cultured epidermal autograft placed over vascularized Integra,⁴⁰ preseeded keratinocytes into the Integra, and applied in a single stage.^{41–44}

Dermagraft

Dermagraft (Organogenesis, Canton, MA) is a polyglactin mesh seeded with neonatal fibroblasts. The fibroblasts produce collagen, glycosaminoglycans, fibronectin, and other growth factors. Over time the mesh is resorbed and replaced with the patient's own tissue.³⁷ Dermagraft has applications as both a temporary and permanent covering to increase the successful take of meshed split-thickness skin grafts on excised burn wounds and for venous ulcers and pressure ulcers.^{37,45} With respect to infection, exudate, healing time, time to closure, and graft take, Dermagraft has been shown to be equivalent to allograft.^{45–47}

Apligraf

Apligraf (Organogenesis, Canton, MA) is a bilayered skin-equivalent. The lower "dermal" layer consists of type I bovine collagen and fibroblasts obtained from neonatal foreskin. The upper "epidermal" layer is derived from keratinocytes. It has to be applied "fresh" and has a shelf-life of 5 days at room temperature.³⁷ It has been used to cover and help heal venous ulcers and diabetic foot ulcers. It has been used as a temporary covering over meshed expanded autograft for excised burn wounds.⁴⁸

Bioprosthetic mesh

To avoid the possible side effects of synthetic prosthetic mesh and provide a more biocompatible material, bioprosthetic materials have been developed and used for multiple

BOX 30.4 Characteristics of the ideal bioprosthetic mesh

Resistance to bacterial colonization and chronic infection

Biocompatibility and noncarcinogenicity

Available readily at acceptable cost

Ability to withstand physiological stresses over a long period of time

No additional pain caused after implantation

Promotion of strong tissue ingrowth

Avoidance of substantial contraction or expansion after implementation

Limits development of adhesions to visceral structures induced

Provides cells with a supportive framework and the necessary signals for host cells to grow, differentiate, and interact, while at the same time it should become remodeled as the wound gains strength and new tissue is formed

(Adapted from Bellows CF, Alder A, Helton WS. Abdominal wall reconstruction using biological tissue grafts: present status and future opportunities. *Exp Rev Med Devices*. 2006;3:657–675.)

applications. Currently available bioprosthetic mesh materials are derived from decellularized mammalian tissues, either human (allogeneic) or animal (xenogeneic). Dermis is the most common source tissue for bioprosthetic meshes. Bioprosthetic mesh materials are processed to remove cells, cellular debris, and other potentially immunogenic components optimally without disrupting the native extracellular matrix (e.g., collagen, proteoglycan) architecture. Preservation of the native extracellular matrix is important to allow these materials to remodel and regenerate (gradually being replaced with native host tissue) rather than become scarred and encapsulated by the body. An ideal mesh should possess the characteristics shown in [Box 30.4](#).

There are a growing number of bioprosthetic mesh materials available from which the surgeon can select. Many of these materials are used for complex torso reconstruction, including breast reconstruction, chest wall reconstruction and ventral hernia repair.⁴⁹ They are often selected over synthetic mesh owing to their ability to resist infection.⁵⁰ They limit repair site adhesions^{51,52} and tolerate cutaneous exposure, usually without the need to remove the bioprosthetic mesh.

Small intestinal submucosa

Small intestinal submucosa (SIS) (Biodesign, Cook Biotech, West Lafayette, IN) is a biomaterial created from the small intestine of pigs. After removal of the mucosal, serosal, and muscular layers of the small intestine, a strong, collagenous matrix remains. The submucosa of the small intestine provides mechanical strength to the intestine. The strong, yet biochemically rich and diverse extracellular matrix of the submucosa makes it an excellent choice for a naturally derived biomaterial. First described as a vascular graft in 1989,⁵³ SIS has been applied to over 20 applications in humans, including multiple types of hernia repair,^{54–56} dural repair,⁵⁷ bladder reconstruction,^{58,59} and stress urinary incontinence treatment.⁶⁰ Originally released in 1989 as Surgisis, this biomaterial has undergone several revisions to allow better integration of the host tissue. In 2008, it was renamed

Biodesign to reflect the significant improvements that had been made to the biomaterial.

Human acellular dermal matrix

Human acellular dermal matrix (HADM) (AlloDerm, LifeCell, Branchburg, NJ; Allomax, Bard Davol, Murray Hill, NJ; and FlexHD, Ethicon360, Somerville, NJ) is made from donated allograft human dermis. Each manufacturer has a proprietary technique for producing the acellular dermal matrix. In general the epidermis and subcutaneous tissue are removed and the dermis is processed, with either freeze-drying or chemical detergents, resulting in the collagen structure of the dermal matrix. Applications of HADM include implant-based breast, abdominal wall, chest wall, and pelvis reconstruction, and lip augmentation. Micronized HADM (Cymetra, LifeCell, Branchburg, NJ) is also available and has been used for laryngoplasty and as a soft-tissue filler.

Porcine acellular dermal matrix

Porcine acellular dermal matrix (PADM) has been developed for applications similar to HADM. Porcine materials are more abundant and it is easier to control the harvesting conditions. However, because the PADM is from a xenogeneic source, additional processing must occur to prevent an adverse immunogenic reaction when implanted in humans. To inhibit immunogenicity and reduce collagenase-dependent matrix degradation, first-generation PADM (CollaMend, Davol Bard, Warwick, RI and Permacol, Covidien-Medtronic, Minneapolis, MN) undergo intentional chemical cross-linking of collagen fibers during the manufacturing process. A secondary side effect of the cross-linking is the alteration of the extracellular matrix structure, which has been shown to inhibit cellular infiltration, revascularization, and matrix remodeling potential.⁶¹

A newer generation of PADM (Strattice, LifeCell, Branchburg, NJ), is processed without chemical cross-linking. In this case, the [galactose- α (1,3)-galactose] antigen, which is the major cause of the immune response associated with acellular xenografts, is enzymatically removed.

It is not entirely clear which of these products has a better outcome; however, in a recent *in vivo* animal study comparing cross-linked PADM to noncross-linked PADM for abdominal wall reconstruction, the noncross-linked PADM was rapidly infiltrated with host cells and vessels while cross-linked PADM became encapsulated. Noncross-linked PADM had weaker adhesions to repair sites while it increased the mechanical strength of the bioprosthesis-musculofascia interface at early timepoints. Thus, the study concluded that noncross-linked PADM may have early clinical advantages over cross-linked PADM for bioprosthetic abdominal wall reconstruction.⁶² However, no comparative human studies have been performed to date.

Other bioprosthetic mesh products

Bovine pericardium (Veritas, Baxter Healthcare Corp., Deerfield, IL) collagen matrix is a noncross-linked bovine pericardium. The decellularization and reduction of the immunogenicity are achieved by capping free amine groups using a proprietary chemical process.

Bovine fetal dermis (Surgimend and Primatrix, Integra Life Sciences (formerly TEI), Plainsboro, NJ) is an acellular dermal matrix derived from fetal calves. It is not cross-linked and can facilitate cell penetration, revascularization, and integration with host tissues.

Amniotic/placental-based materials

Amnion has been used as a biomaterial for over 100 years. Its first published use as a skin graft occurred in 1910 and its first use in burn patients in 1912.^{63–65} The amniotic membrane is a monolayer of epithelial cells, a thick basement membrane, and an avascular matrix. This epithelium manufactures multiple cytokines and growth factors. The amnion has been reported to promote epithelialization while maintaining antimicrobial, immunogenicity, and analgesic properties. Many of the properties are preserved even after de-epithelialization and sterilization of the amnion. Due to these factors, amnion has biological and mechanical properties that make it useful as a valuable dressing material.^{63,66} Over the past few years several companies have developed products derived from either human placental, amniotic or chorionic tissue. BioFix (Integra LifeSciences, Plainsboro, NJ) and AmnioFix (MiMedx, Marietta, GA) are sterile, dehydrated and decellularized amniotic membrane. They are used to cover wounds and to fill tissue defects. BioFix Plus (Integra LifeSciences, Plainsboro, NJ) and EpiFix (MiMedx, Marietta, GA) are similar products but these also include the chorion. These products require no preparation and can be placed on the wound with either side up. One of these companies has also released a particulate human decellularized placental connective tissue matrix (BioFix Flow, Integra LifeSciences, Plainsboro, NJ). This product comes in a syringe and is designed to

be used as an injectable connective tissue matrix. All of these products are stored at room temperature with a 5-year shelf-life. Grafix (Osiris Therapeutics, Columbia, MD) is a cryopreserved placental membrane, which, like the products mentioned above, is made up of extracellular matrix and growth factors/cytokines. However, this product also contains cells native to the tissue (which include epithelial cells, fibroblasts, and stem cells). It is used to help heal wounds. As it is a frozen product, it needs to be thawed prior to being used.

Future materials

Biomaterials and implants have made huge impacts on medicine and surgery. Some implants are designed to have as little impact or interaction with the body as possible. Others are designed to interact with the body in a passive way (e.g., biodegradable PLGA polymers). The most recent biomaterials are being designed to modulate their environment to create a tissue-specific response. Furthermore, hybrid biomaterials containing cells, polymers, and growth factors are currently being developed in *in vivo* models. These biomaterials will eventually be able to “sense” their surroundings and change their biochemical and mechanical properties in response to the needs of the environment. As with the past development of biomaterials, the continued progress of the biomaterial field depends upon an interdisciplinary collaboration between engineers, scientists, clinicians, and industry. With continued cooperation between these biomaterials experts, the future use of biomaterials and implants in plastic surgery will likely change significantly in the future. The goal would be to manufacture materials with specific properties to reconstruct site-specific defects individualized to the exact biologic, chemical, and functional needs of the reconstruction.



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Facial prosthetics in plastic surgery

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SYNOPSIS

- The success of osseointegration biotechnology has revolutionized facial prosthetic reconstruction.
- Titanium is the implant material of choice as it is light, biocompatible, and resistant to corrosion.
- Implant placement technique is crucial to produce bone–implant contact with no interposed fibrous tissue and successful bone healing.
- Appropriate treatment selection requires understanding of all options available.
- Multidisciplinary team planning is required.
- Osseointegration biotechnology provides plastic surgeons with more treatment options for challenging head and neck deformities.

Deformities in the head and neck region can have a profound effect on the function, aesthetics, and psyche of an individual. Considerable time, effort, and ingenuity have been spent trying to develop meaningful reconstructive solutions to a wide variety of craniofacial defects. Autogenous reconstruction remains the gold standard, but in certain cases, autogenous reconstruction may be contraindicated, technically impossible, or have the potential to solve the reconstructive issues only partially.

Historically facial prosthetics have been of limited benefit. Retention of facial prostheses has been largely unsuccessful because of the need for adhesives or crude mechanical means of maintaining retention. The patient lacked confidence about the positioning of the prosthesis and its ability to stay in place. Often associated pain or discomfort would limit the length of time and circumstances in which the prosthesis would actually be worn. The adhesives are those used in industry and were not developed for the unique sensitive human biological environment. They often had adverse effects on the underlying skin compromised by radiotherapy, trauma, or thermal injury¹ and affected the durability and longevity of the prosthesis.

With the success of osseointegration and its ability to solve the problem of prosthetic retention,^{2,3} a new treatment

modality was now available.^{4,5} Prosthetic longevity is increased without the need for adhesives.^{6,7} Osseointegrated facial prosthetics now meet the necessary criteria for success: (1) aesthetic acceptability; (2) functional performance; (3) biocompatibility; and (4) desired retention.⁸ The use of osseointegration biotechnology in facial prosthetic restoration has been hailed as the most significant advance in the field of facial prosthetics in the past 28 years.⁹ It is estimated that more than 90 000 implants have been installed extraorally in more than 45 000 patients up to the year 2007.¹⁰ Craniofacial osseointegrated reconstruction gives the plastic surgeon another viable treatment option in many challenging head and neck defects.¹¹ It can provide some patients with a meaningful and enhanced quality of life when in the past other treatment options would not have been successful. Unfortunately, competing specialties or providers have presented autologous techniques and craniofacial osseointegration as unrelated technologies.¹² Osseointegrated and autogenous techniques should not be viewed as competing technologies, but rather as complementary reconstructive procedures that optimize the opportunity for success in the management of major head and neck deformities.

Why this situation has arisen is unclear. In some cases, it appears to be due to a lack of understanding of osseointegration and its benefits. It may be viewed only as a salvage procedure when all else has failed and both the patient and surgeon are desperate. It is not viewed as “real” surgery, only as throwing a few screws in the bone. Those in doubt cannot understand how patients would be satisfied with a prosthesis, “a foreign object that never becomes part of their body image”. To any surgeon with experience in osseointegration, these lines of thinking are seriously flawed.

This intervention requires long-term support by both the caregiver and the funder for maintenance of the implant sites as well as future prosthetic construction. It is analogous to the time and financial commitment required in an organ transplantation program.

Historical perspective

Historically, implants in bone were largely unsuccessful and had a poor reputation for long-term success. In the 1950s, Professor Brånemark, from Goteborg, Sweden, discovered titanium behaved somewhat differently from other metals when in contact with bone. The term “osseointegration” was coined by Brånemark in 1977.¹³ It is defined as the direct contact – structural and functional – between ordered living bone and the surface of a load-bearing implant. Osseointegration is a dynamic process that involves micromodeling at periosteal and endosteal surfaces and remodeling at the bone–implant interface.^{8,10,14} This principle of osseointegration ultimately led to the development of successful dental implants.¹⁵ The first osseointegrated implant was placed in a human in 1965. Albrektsson *et al.* further postulated that a skin-penetrating implant may be possible.¹⁶ Implants were first placed in the mastoid region to support a bone-anchored hearing aid in 1977 and to retain an auricular prosthesis in 1979¹⁷ (Fig. 31.1). Subsequently, numerous reports have confirmed the efficacy and predictability of craniofacial osseointegration.^{18,19} The concept of anchoring craniofacial prostheses on osseointegrated implants was accepted by the Food and Drug Administration (FDA) in 1985. The FDA accepted the concept of anchoring hearing aids on implants in adults in

1995 and children in 1998. In 1985, implants were used in hand surgery to anchor joint replacements and in the early 1990s the concept was used for anchoring prostheses in amputees’ fingers, hands, arms, and legs.

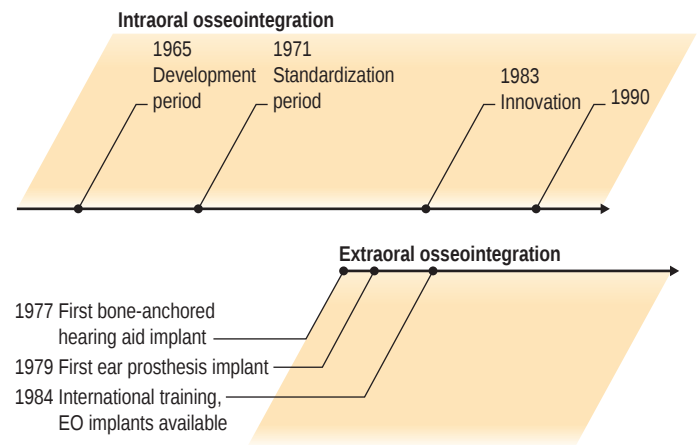


Fig. 31.1 Historical development of osseointegration biotechnology. Through the Brånemark experience, osseointegrated implants have been subjected to over 30 years of scientific scrutiny. Craniofacial applications were first introduced in 1977. EO, extraoral.

BOX 31.1 Advantages of craniofacial osseointegration⁷

Procedures short
 Minimal morbidity
 Minimal postoperative pain
 Outpatient procedures
 Short learning curve
 Allows examination of tumor resection site
 Salvage of autogenous failures
 Use in compromised tissues
 Excellent prosthetic aesthetics

BOX 31.2 Disadvantages of craniofacial osseointegration⁷

Need for multidisciplinary team
 Need for reliable, committed patient
 Ongoing expense of prosthetic remakes and maintenance visits
 Not one's own tissue

Access the Historical Perspective section and Fig. 31.1 online at
<http://www.expertconsult.com>

Advantages of craniofacial osseointegration

Craniofacial osseointegration has many advantages (Box 31.1).²⁰ The surgical procedures are generally short with minimal morbidity and are performed on an outpatient basis. There is a short learning curve and results are predictable. The patients usually have minimal postoperative discomfort. Examination of the tumor resection site is easy and allows early diagnosis of any tumor recurrence.

Craniofacial osseointegration can successfully salvage a patient with a failed autogenous reconstruction and often offers superior aesthetics. When compared with adhesive-retained facial prosthetics, osseointegration offers predictable prosthetic retention, increased prosthetic durability and lifespan, enhanced prosthetic aesthetics, ease of displacement, no underlying skin damage, successful incorporation of the prosthesis into the body image, and a happier, more satisfied patient. Osseointegration can also be considered in diabetics and smokers.

The disadvantages of craniofacial osseointegration include the need for a larger multidisciplinary team with skills that are often not freely available. Patients also require regular maintenance visits and a new prosthesis every 2–5 years (Box 31.2).²⁰ Lifetime ongoing costs can be an issue with some insurance companies.

Indications for craniofacial osseointegration

Craniofacial osseointegration can be of particular benefit for reconstruction of selected defects involving the ear, orbit, nose, and combined midfacial defects. The osseointegrated implants have also been used to secure hairpieces.²¹ A newer application of interest to the plastic surgeon is the use of a bone-anchored hearing aid (BAHA) in children with microtia. In the past concern has been expressed combining a BAHA and an autogenous ear reconstruction. Fear of inappropriate positioning of the implant adversely affecting future autogenous ear reconstruction usually prevented patients having the benefits of both treatment modalities. This usually resulted in the BAHA being placed too far posterior or not being considered at all. Certainly the BAHA is an excellent option for hearing restoration in bilateral microtia patients and more recently has proven of benefit in unilateral microtia patients (Fig. 31.2). It is a much more straightforward, safe, and predictable way of improving hearing than previous autogenous means of canalplasty and middle-ear reconstruction.¹⁰

Ear reconstruction

Autogenous reconstruction of auricular defects has improved greatly in the latter half of the 20th century because of the work of pioneers such as Tanzer,²² Brent,^{23–26} Fukada and Yamada,²⁷ Cronin,²⁸ Bauer,²⁹ Yanai *et al.*,³⁰ Isshiki *et al.*,³¹ Nagata,^{32–34} and others. Certainly, not all reconstructive attempts are successful. The appropriate treatment selection for major ear defects continues to be controversial (Table 31.1).²⁰ Certain auricular defects have limited autogenous



Fig. 31.2 Bone-anchored hearing aid (BAHA) and autogenous ear reconstruction for microtia.

Table 31.1 Indications for osseointegrated ear reconstruction ⁷	
Definitive	Relative
Major cancer resection	Microtia – most controversial
Radiotherapy	Absence of lower half of the ear
Severely compromised tissue	Calcified costal cartilage
Patient preference	
Failed autogenous reconstruction	
Potential craniofacial anomaly	
Poor operative risk	

BOX 31.3 Indications for osseointegrated nasal reconstruction ¹⁰
Failed autogenous reconstruction
Scarring at autogenous donor sites
Reconstruction following autogenous reconstruction because of tumor recurrence
Patient preference
Medical contraindication to multistaged autogenous reconstruction

options, particularly after removal of the ear for cancer with associated radiotherapy. It is our belief that these reconstructive techniques are complementary and must be presented in this manner.^{8,12,20} Definite indications for osseointegrated auricular prosthetic reconstruction include: (1) following major cancer resection; (2) radiotherapy to the proposed site of auricular reconstruction; (3) severely compromised local tissue (Fig. 31.3); (4) patient preference; and (5) salvage procedure for failed autogenous reconstruction. Relative indications include: (1) microtia; (2) absence of the lower half of the ear; and (3) patients with calcified costal cartilage.

Probably the most controversial indication for osseointegrated auricular reconstruction is microtia in children. Although it is technically possible to place implants in children as young as 3 years of age and early results are encouraging, the follow-up in these situations is short. Because the use of craniofacial osseointegrated implants requires removal of any local ear remnants and produces scarring in the operative field, future autogenous reconstruction options are very limited. For these reasons, the use of osseointegrated auricular reconstruction in the pediatric age group requires very careful consideration by the clinician and family (Fig. 31.4). A publication by Zeitoun *et al.*³⁵ outlines the difficulties seen using

osseointegration in the pediatric population. It also showed an increased need for psychological support in many of these patients. Our approach is to offer autogenous ear reconstruction to pediatric patients with microtia. Despite the potential for difficult treatment selection decisions, we rarely find this to be the case. Patients usually decide quite quickly after the possibilities are discussed. It is rare for patients to change their mind following further discussion.

The use of an adhesive-retained auricular prosthesis is very limited and almost relegated to historical significance only. It certainly cannot be considered a “test” for an osseointegrated prosthesis. It offers none of the major advantages of implant-retained prostheses such as ease of placement, predictable retention, improved aesthetics, increased lifespan of the prosthesis, and no ongoing insult to the skin.

Osseointegrated nasal reconstruction

Indications for osseointegrated nasal reconstruction include: (1) failed autogenous reconstruction; (2) significant scarring in potential autogenous donor sites;⁶ (3) tumor recurrence following initial autologous reconstruction; and (4) patient preference (Box 31.3). Because of the need for multiple

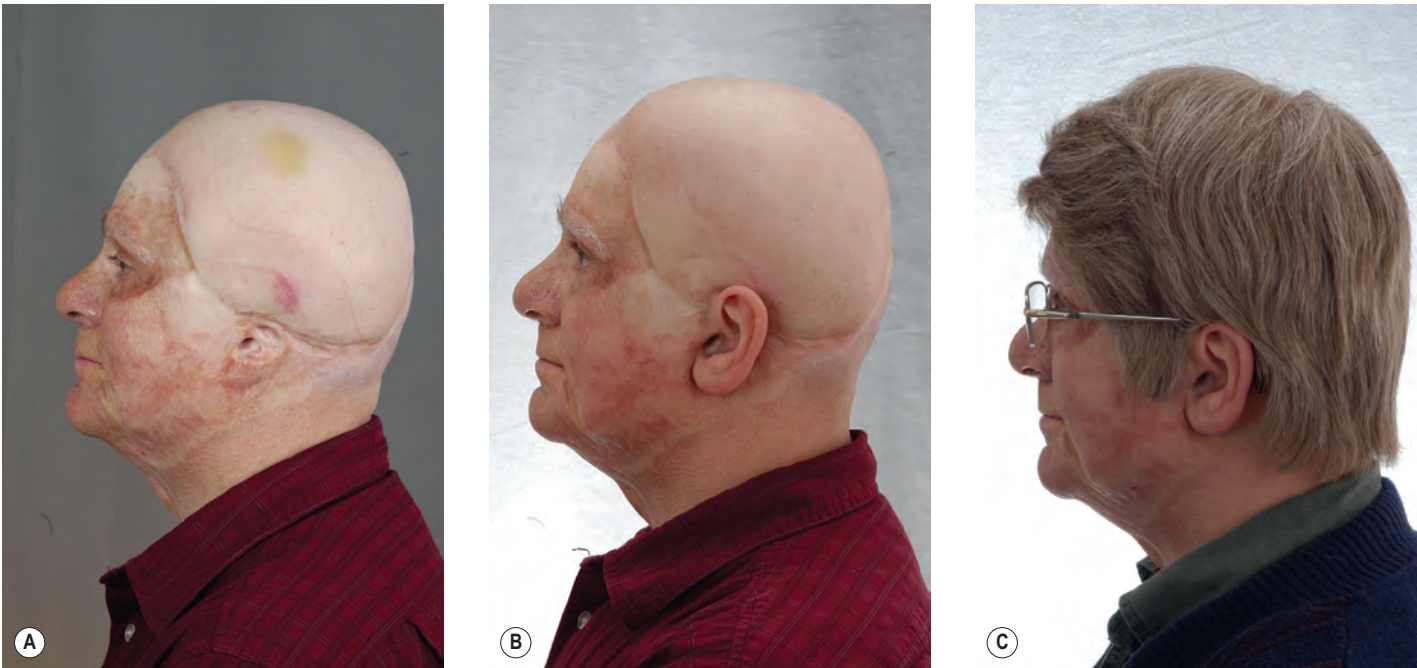


Fig. 31.3 (A–C) Reconstruction following severe electrical injury included cranioplasty, free-flap scalp coverage, and ear reconstruction with implant-retained prosthesis.



Fig. 31.4 (A,B) Ear loss and severe local tissue trauma secondary to dog attack in a child. Reconstructed with implant-retained prosthesis.

surgical stages and the greater variability in the ultimate result with autogenous reconstruction, many patients with total nasal loss opt for placement of implants and a nasal prosthesis (Fig. 31.5). Certainly, there is less surgery involved with less morbidity. There is no need for other donor sites, and tumor surveillance is easy with prosthesis removal.⁸ The application of “nontraditional” long zygomatic implants may be useful in difficult situations of nasal reconstruction.³⁶

Osseointegrated orbital reconstruction

Patients with loss of the orbit and orbital contents have very poor autogenous reconstructive options (Box 31.4). Although autogenous coverage may be necessary to cover important neurological structures, in many cases it is provided only to fill the residual orbital cavity. However, “filling the hole” does not create an aesthetic result. It is in these situations that

BOX 31.4 Indications for osseointegrated orbital reconstruction

- Loss of orbit and orbital contents
- Severe enophthalmos with compromised vision
- Difficulty with an ocular prosthesis and significant eyelid distortion secondary to trauma or radiotherapy that is not amenable to autogenous correction

osseointegrated orbital reconstruction clearly has advantages over autogenous reconstruction (Fig. 31.6). The aesthetic results are far superior and again allow visualization for early tumor recurrence. This approach could also be considered in patients with severe enophthalmos and significantly compromised vision. Less frequently, it can be considered in patients with an ocular prosthesis and significant eyelid distortion

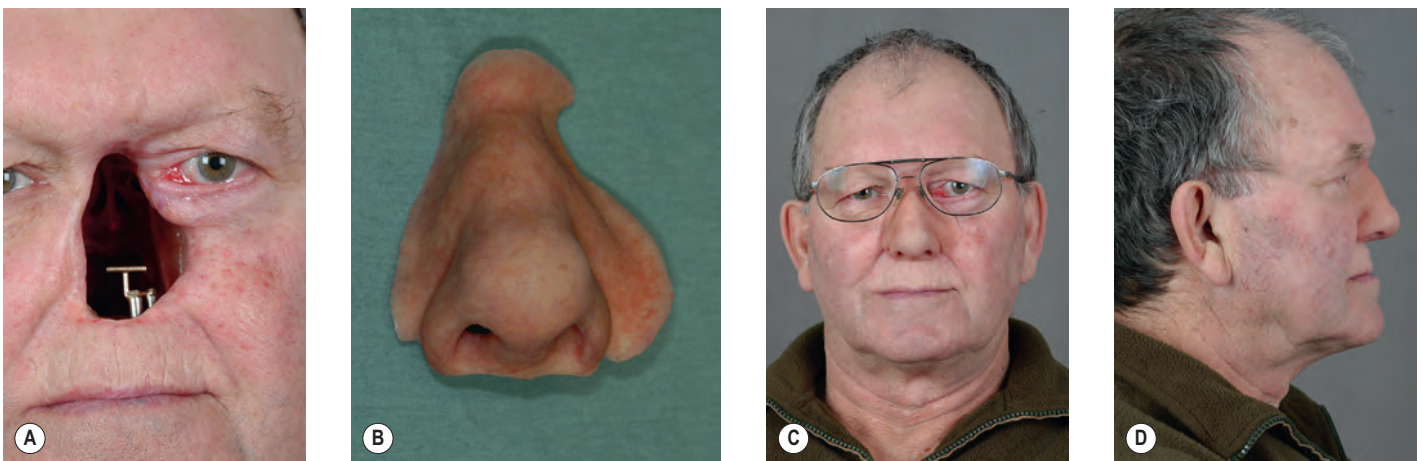


Fig. 31.5 (A–D) Nasal deformity following cancer resection reconstructed with implant-retained nasal prosthesis.



Fig. 31.6 (A,B) This patient had an orbital exenteration for a neurofibroma of the orbit and scalp and was reconstructed with latissimus dorsi free flap and skin graft. Further reconstruction using an implant-retained orbital prosthesis achieved a more aesthetic result.

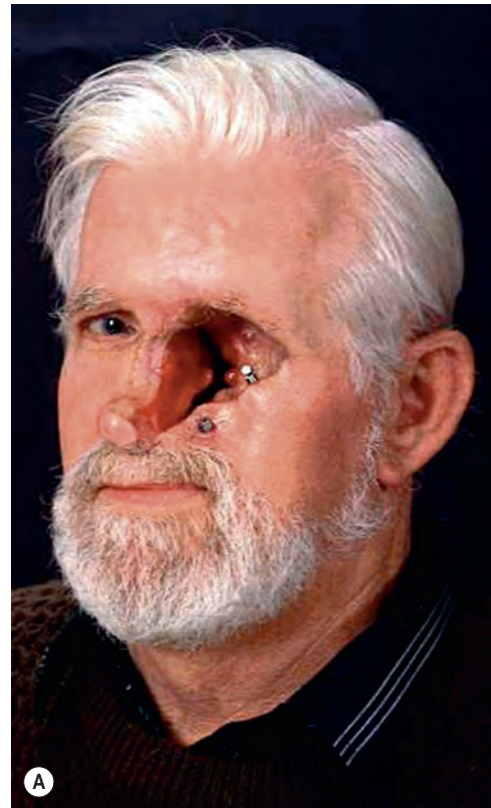


Fig. 31.7 (A,B) This patient had an extensive basal cell carcinoma invading his orbit, nasal region, and maxilla. After surgical extirpation, implants were later placed and a naso-orbital prosthesis constructed. Autogenous options were poor.

secondary to trauma or radiotherapy that is not amenable to autogenous correction. The hope for the future would be to create an orbital prosthesis that can mimic movement of both the lids and globe of the opposite normal eye.¹³

Midfacial reconstruction

Patients with complex facial defects that may include the orbit, nose, and maxilla again have poor autogenous options (Fig. 31.7). Craniofacial osseointegration offers significant advantages. It enables examination of the postsurgical

oncologic defect and allows for a very acceptable aesthetic result. In the patient shown in Fig. 31.7 it allowed early detection of a recurrence on the posterior orbital wall. Treatment consisted of surgical removal and reconstruction with a temporoparietal fascial flap and skin graft. The patient was able to resume wearing his prosthesis again only 12 days after surgery to resect the recurrence. Extraoral osseointegration in combination with intraoral osseointegration may also result in significantly improved functional results over conventional prosthetic or autogenous techniques.

In some cases the extent of resection, the nature of the reconstruction, and the quality and quantity of remaining bone or patient preference may make an implant retained prosthesis impractical or undesirable. Other means of retention may be used to hold a prosthesis in place with reasonable aesthetic and functional results (Fig. 31.8). This could also be a treatment alternative in a select group of patients being considered for composite tissue allotransplantation or as an interim measure prior to CTA.

Factors important to obtain osseointegration^{13,37}

Choice of implant material

Many materials have been considered for osseointegration. Although other metals such as vanadium, tantalum, aluminum hydroxide, and ceramics like hydroxyapatite are known to integrate with bone to a certain degree, titanium is currently the material of choice.³⁷ Titanium is relatively light but stiffer than bone. Its springiness allows it to flex with the bone. The most important factor is the ability of its

titanium oxide layer on the implant surface to react with the adjacent bone (its biocompatibility). The key to success is what happens at this implant–tissue interface. The most successful is commercially pure titanium, which is 99.75% pure. This differs from the most commonly used titanium alloy, which contains 90% titanium, 6% aluminum, and 4% vanadium, and exhibits much less satisfactory characteristics of osseointegration.

Implant–tissue interface

Except for mechanical forces, all interactions between the implant and host occur from physiochemical forces less than 1.0 mm from the surface. When the titanium implant is exposed to oxygen and comes in contact with the host, a layer of oxide is rapidly formed. It acts as a protective barrier and prevents direct contact between the metal and its environment. The titanium oxide layer continues to grow with time and creates a dynamic interface. The oxide layer is the bioactive component of the implant. The microsurface characteristics of the implant itself, including roughness, porosity, and thread design, all influence its potential for successful osseointegration. A surface roughness of 100 μm or greater is advantageous; an implant that has a very smooth surface will result in poor integration, but with minor bone resorption. A very rough surface will result in rapid integration, but secondary inflammation and resorption that can jeopardize integration later on.

The macrostructure of the implant has importance for integration. Rounding the outer edges and spaces of a threaded implant relieves stress concentration. A screw-shaped implant often shows good primary stability, whereas a cone-shaped implant might be lost because of initial micromovements and hence poor stability.

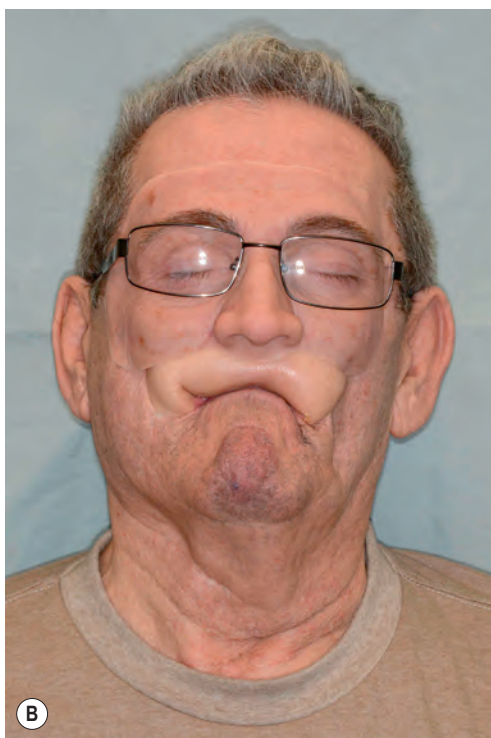


Fig. 31.8 (A,B) This patient had a recurrent basal cell carcinoma resulting in resection of both orbits and the anterior maxilla. After reconstruction with free fibular and radial forearm flaps, a facial prosthesis retained by anatomical undercuts and eyeglasses was created as the patient did not wish to proceed with osseointegration.

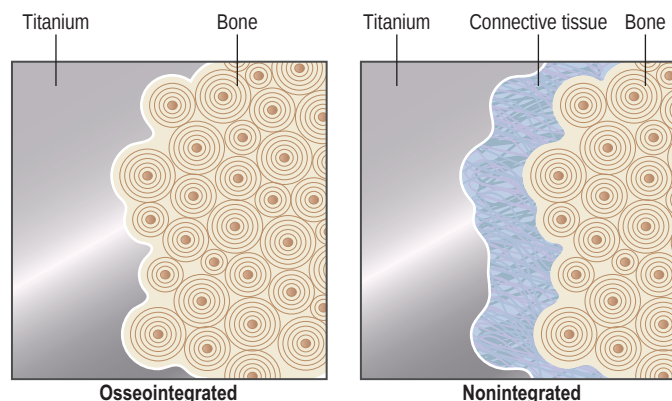


Fig. 31.9 Bone–titanium interface with only oxide layer and no interposed soft tissue.

Bone bed

The bone bed into which the implant is installed is of importance. There is a difference if the implant is installed in a child with relatively soft and immature bone, compared with an adult. The older patient with osteoporosis will integrate the implant to a lesser degree, and implant failure rates have been higher. Patients who have been irradiated or sustained burns will have an altered texture of bone that will reduce the capacity to integrate implants.

Bone preparation

Meticulous, gentle surgical technique is vital for osseointegration to occur.¹⁰ Bone preparation must result in new bone healing around the implant with no interposed fibrous tissue formation and minimal bone necrosis (Fig. 31.9). Proper bone healing results in bone ultimately being in intimate contact with the titanium oxide layer. Sharp drill bits, copious saline irrigation, and slower drilling speeds are required for success. Studies have shown temperatures of 89°C occurring with high-speed drilling despite cooling.^{38–40} Bone exposed to temperatures greater than 47°C for 1 minute showed decreased new bone formation. Exposure to 44°C showed no negative effect. The fixture should only be handled by titanium instruments and never touched by the gloved hand. It is further important that the surgical field should be protected from fibers, powder, and other substances that might hinder osseointegration. At the junction of the titanium oxide and bone, a layer of ground substance consisting of proteoglycans and glycosaminoglycans forms. The thickness of this layer is inversely related to the strength of integration of the bone with the implant.

Traumatic surgery and an implant bed of low healing potential are said to be primary factors limiting successful osseointegration. Implant mobility, overloading, and poor implant biocompatibility are considered to be secondary factors in failure of osseointegration. With successful osseointegration, the weakest portion of the osseointegrated bone–implant complex is the bone itself. After successful osseointegration, attempting to remove an implant will result in failure within the surrounding bone, not at the implant–bone interface.

Implant load

The load of the implant should preferably be in the longitudinal direction. It is important to avoid rotational or cantilever

forces once the implant has integrated. If forces are distributed in the longitudinal direction, even very high loads can be withstood by the implant during many years of function.

Treatment planning

Providing craniofacial osseointegration care requires a larger multidisciplinary team than autologous reconstruction. The core team should include appropriate surgical expertise, including plastic surgery, otolaryngology, and oral surgery, a prosthodontist, an anaplastologist, and appropriate nursing and dental assistants. Careful preoperative assessment and planning are crucial for the ultimate success of this clinical endeavor. Only by having the full spectrum of team members can the patient be presented with all appropriate options to make a truly informed decision.

The treatment-planning process starts with a multidisciplinary consultation. Team members then formulate an approach to each individual patient's problem. The preoperative workup includes charting, standardized preoperative photographs and psychological profile. Preoperative assessment allows an evaluation of bony sites for implant placement, the presence of surrounding vital structures, general quality of the bone, and overlying soft tissues. Radiologic examination, impressions of the defect and the corresponding normal side, and three-dimensional images may be used during digital treatment planning, medical modeling, and construction of surgical templates.^{41–43}

The patient should have no systemic or local factors that could significantly influence bone-remodeling capacity.⁴⁴ Age alone is not considered a contraindication. Patients as young as 3 years of age or in their 80s have been successfully treated. There should be no psychiatric or substance abuse conditions. Smoking is a relative contraindication,⁴⁵ as is radiotherapy,^{10,46,47} or chemotherapy.⁴⁸ The literature on smoking and implant survival involves dental implants and not craniofacial osseointegrated implants.⁴⁹ A past history of radiotherapy requires assessment for hyperbaric oxygen treatment before and after implant placement to optimize the chance for successful osseointegration.^{50–52} Patients must have a certain level of cognitive, visual, and dexterous ability to maintain osseointegrated implants. They must also have reasonable geographic accessibility to an osseointegration unit. Once the preoperative workup and informed consent have been obtained, treatment can begin.

In autologous reconstruction, the surgeon provides the final result. This differs from osseointegration, where the surgeon sets the stage for the final prosthetic result by the prosthodontist or anaplastologist. This makes preoperative planning and proper implant placement even more vital to ultimate treatment success. Good communication between the surgeon and prosthodontist or anaplastologist preoperatively and often intraoperatively is critical. Implants placed in the wrong position will compromise the final aesthetic and functional result or make further implant placement necessary.

Surgical technique

The surgical approach as developed by Brånemark is a meticulous multistep technique that may be performed in one or two stages, depending on the clinical situation.⁵³ Although

titanium is used by many specialties in many clinical situations, this application resulting in osseointegration should not be confused with these other uses of titanium. Osseointegration biotechnology is very specific in terms of osseointegration fixture production and preparation, surgical technique, and final surgical result. Other implant systems (Conexão, Otorix, Straumann, ITI, Southern) are available but are principally based on the original implant.¹⁰

Compared to intraoral osseointegration, the fixtures for extraoral use tend to be shorter (3–5 mm). The length of implant used depends on the particular bone thickness. Longer fixtures can sometimes be used in the frontal bone, zygoma, and maxilla. Ideally bicortical purchase is obtained if anatomically possible. The extraoral environment tends to be a more hostile, less forgiving environment than the protected intraoral situation. The gingiva is constructed to have mucosal penetration; saliva and the cleaning action of the tongue are quite beneficial in keeping the abutments clean. Penetration through skin with nearby hair, muscle, and sebaceous glands lends itself to the development of more soft-tissue problems. The skin does not attach to the implant abutment and is essentially maintained as an open wound. The ability to modulate this interface better would result in fewer local skin problems.

Surgery can be performed in one or two stages.^{1,12} The one-stage procedure is usually reserved for adult patients with good bone quality and quantity. The surgery can be performed either under general anesthesia or with sedation and local anesthesia.

A treatment template is used to locate the site for implant placement. Appropriate implant positioning is crucial to the ultimate prosthetic success. Digital technologies can be useful for this aspect of treatment planning. Adobe Photoshop or Geomagic Freeform have been used successfully for this purpose (Fig. 31.10). In ear reconstruction, implants should be placed under the future site of the antihelical fold of the ear prosthesis. This is where there is maximal depth to hide the protrusion of the fixture abutments within the prosthesis.

In orbital reconstruction, the implants need to be placed well within the orbital rim rather than anteriorly, where it is technically easier to place them. Again consideration needs to be given to the space requirements of the orbital prosthesis in all three dimensions. Within the orbit, the implant axes should not align to a central converging point because this may make prosthetic procedures very difficult.

In nasal reconstruction, better success is obtained by placing implants into the floor of the nose rather than into the glabellar region. In cases where there are concerns about the underlying bone quality or quantity, a radiological study will be performed (Fig. 31.11). Simplant or Mimics software in combination with a CT scan allows assessment of the bone and surgical simulation of implant placement. Appropriate templates can then be constructed to help the surgeon with the implant surgery.

At surgery the area is infiltrated with a lidocaine (Xylocaine) and epinephrine solution and a skin flap is elevated. The periosteum is exposed and either a periosteal flap is elevated or a circular opening made in the periosteum. A surgical locating template is invaluable in difficult cases to optimize positioning of the implant, minimize the extent of surgical dissection, decrease the number of pilot drill holes needed to find adequate bone, and decrease the duration of the procedure. A 3.0-mm guide drill is used first. If bone is present at this depth after drilling, the drill hole is deepened to 4.0 mm. This drilling is carried out at a speed of 2000 rpm with copious saline irrigation. The base of the guide hole is checked to determine that penetration of underlying vital structures has not occurred.

In the second step, the guide hole is widened with a countersink. A fresh countersink drill is used with copious saline irrigation. This also prepares a flat countersink area on the bony surface for seating of the implant flange. Flangeless fixtures are often placed in the orbital region. Issues with cleaning and accumulation of debris around the implant flange can be problematic and threaten long-term survival of the implant.

The third step involves placing the self-tapping implant. It is placed at a drill speed of 15–20 rpm and 20–40 N-cm torque. All these precautions are taken to minimize bone necrosis. With bone necrosis, fibrous tissue will develop, compromising the tissue–implant interface, and osseointegration will not occur. All drills and countersinks are discarded after each procedure. Craniofacial implants are 3.75 mm in diameter and are available in 3.0, 4.0, and 5.5-mm lengths (Fig. 31.12). The longest implant possible is preferable based on bone depth and quality.

At the fourth step, a cover screw or space screw is placed in the implant. This prevents soft-tissue ingrowth into the central portion of the implant where the abutment will ultimately connect. A space screw fits in the center of the implant and does not increase the profile of the implant during the healing phase.

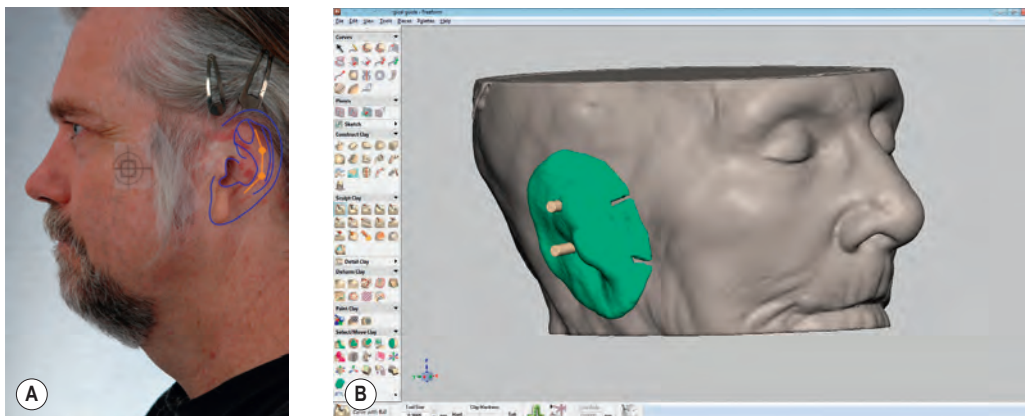


Fig. 31.10 (A,B) An ear template is used to choose the appropriate site for implant placement.

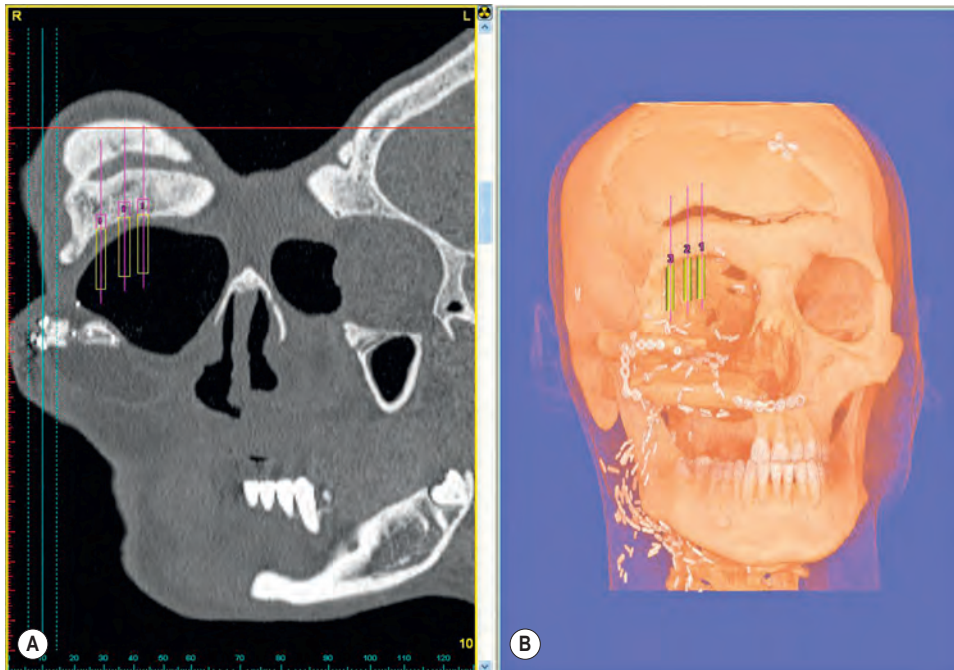


Fig. 31.11 (A,B) A Simplant or Mimics study can be performed to determine quality and quantity of underlying bone.

It is used if implants are placed under an area of existing skin graft or thin skin flap, usually in the orbital region. The surgical incisions are then closed if a two-stage procedure is planned.

If a one-stage procedure is possible, the outer layer of the flap is elevated as an attached split-thickness graft, and underlying soft tissues are removed. The edges around the outside of the flap site are aggressively thinned and the graft is replaced to take on the underlying periosteum. The most common causes of future soft-tissue problems are related to tissue movement around the abutment, and the remaining hair follicles. In non-irradiated tissues, the implants are usually left for approximately 3 months, at which time phase II surgery can occur. In the midface or in patients with a history of radiotherapy, this time period is usually extended to 6–9 months. Usually, two implants are required for auricular reconstruction and at least three implants for orbital reconstruction. Extra implants are often placed as sleepers in the orbital region as the long-term success rates in this region

are not as high as elsewhere. If an implant fails, then a sleeper can be exteriorized, and the patient can continue to wear the prosthesis with minimal interruption.

If a two-stage technique is needed phase II surgery involves exposing the implant, radical thinning of the overlying and surrounding tissue, creation of a hairless, nonmobile zone of 1.0 cm around each abutment, and connection of an abutment to the underlying fixture. Improper soft-tissue surgery is the most common cause of ongoing tissue reaction around the abutment. Other surgical considerations include removal of any residual soft-tissue elements to produce a flat tissue surface for the auricular or nasal prosthesis. More recently there has been success in the mastoid region with one-stage placement of implants under optimal local conditions.^{54,55} Accepted clinical criteria for a one-stage procedure in the mastoid region of older children (>10 years) or adults include:

- no past history of irradiation
- cortical layer of bone greater than 3.0 mm in thickness
- uncomplicated surgery.

The technique is essentially the same as for phase I and II surgery, but both phases are conducted at the same operation. After one-stage surgery, the implant must be protected and not loaded for at least 3 months.



Fig. 31.12 Craniofacial implants and fixtures of commercially pure titanium.

Prosthetic construction

Construction of the prosthesis generally begins 4–6 weeks after phase II surgery or 3–6 months after one-stage surgery when local tissues have healed sufficiently to be a stable base for overlying prosthetic construction. For auricular prostheses a bar superstructure is individually designed and connected to the abutments. Clips on the undersurface of the prosthesis securely attach the prosthesis to the bar and are most commonly used for ears. A magnetic retention system is more commonly used for orbital prostheses and occasionally for auricular prostheses when patient dexterity is limited. The

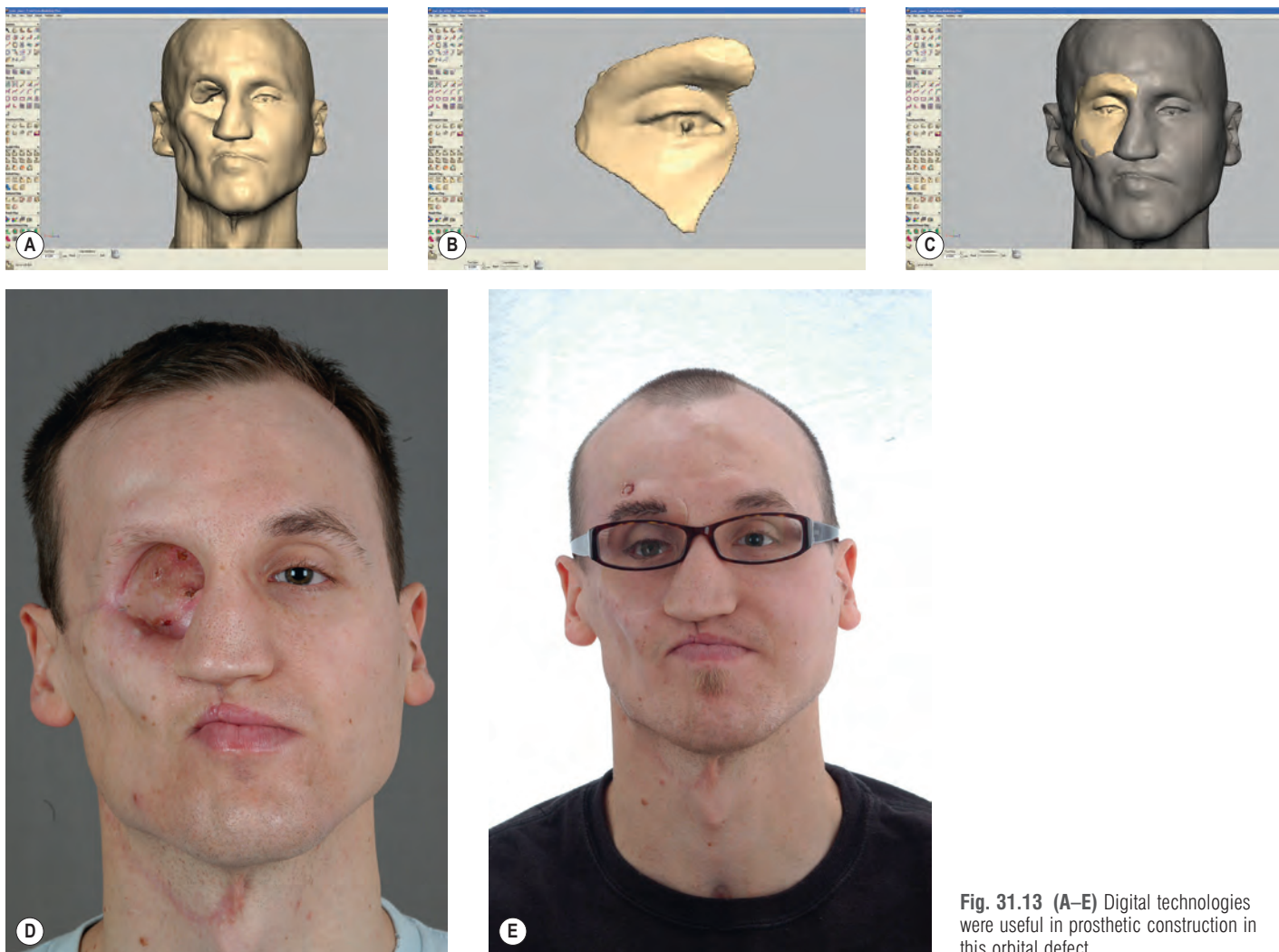


Fig. 31.13 (A–E) Digital technologies were useful in prosthetic construction in this orbital defect.



Fig. 31.14 Two prostheses are made at the same time with different coloration for different seasons and to prevent a crisis if one prosthesis is lost or damaged. There are clips on the undersurface of the prosthesis for secure attachment to the implant-retained bar superstructure.

prosthesis is first sculpted in wax and related to an acrylic resin substructure containing retentive components. When the prosthesis is anatomically acceptable, a mold is constructed and the prosthesis is made from silicone elastomer.

Digital technologies have been helpful in prosthetic construction.⁴¹ Capture of data from the “normal” side can be done from a moulage or scan of the patient. With computer-aided design software (Mimics, Magics, and Freeform), the model is manipulated and the basic form of the prosthesis is easily constructed using 3D printing (Fig. 31.13). This efficiency optimizes the amount of time needed by the anaplastologist with the patient. Constructing the prosthesis using the anaplastologist’s time and skills efficiently is very important, as they are in limited supply.

Another challenge to the prosthodontist and anaplastologist is color-matching based on the patient’s normal pigments and extrinsic influences such as time of year and patient occupation. One of the newer solutions includes the use of spectrophotometry and computerized color formulation technology for color-matching of the prosthesis to the patient.⁵⁶ Patients will sometimes have summer and winter prostheses to account for subtle pigmentary changes. Many small details and techniques are used to add realism to the prosthesis. Ideally, two prostheses are made at a time (Fig. 31.14). This

BOX 31.5 Ancillary soft-tissue procedures combined with craniofacial osseointegration

Soft-tissue expanders
Scar revision
Free vascularized bone graft
Pedicled bone graft
Alar repositioning
Ectropion repair
Eyebrow reconstruction
Browlift
Static facial sling
Repositioning external auditory meatus
Onlay cartilage graft
Muscle flap
Bone contouring
Rhytidectomy
Tragal reconstruction

prevents a crisis situation if something happens to one of the prostheses. A magnetic retention system is more commonly used for orbital prostheses.

Maintenance program

The long-term success of osseointegration requires an effective ongoing maintenance regimen, analogous to the follow-up in an organ transplantation program. Strong patient commitment is required for success. In particular, conscientious care of the periabutment area is crucial. This includes gentle cleaning on a daily basis, as well as diligent application of appropriately prescribed topical agents (Fig. 31.15) including antibiotic ointment or topical steroid. Our protocol includes a lifetime maintenance recall schedule to impress on them their commitment, which is vital to long-term success. Maintenance visits include assessing the periabutment region, measuring soft-tissue height, checking for tissue reaction, and monitoring the mechanical integrity of the implant–abutment assembly. New prostheses are constructed as needed. The life of an individual prosthesis can vary from 1 to 5 years depending on extrinsic factors such as general care and exposure to sunlight or cigarette smoke.⁶

Ancillary autogenous procedures

It is our belief that treatment of the patient's craniofacial defect is often best managed by a combination of osseointegration and autogenous procedures to optimize the final results (Box 31.5; Figs. 31.16 & 31.17).^{57,58} The goal of the ancillary procedures may include decreasing the size of the facial prosthesis, placing prosthetic margins at junctions of aesthetic units, decreasing the size of the maxillary obturator, improving facial contour, improving symmetry, and bringing viable



Fig. 31.15 Requirements for care at abutment sites.

bone for implant placement into a region compromised by surgery or radiation.

Craniofacial osseointegration outcomes

To evaluate the success of craniofacial osseointegration, several parameters need to be studied.^{59,60} Success from a patient's perspective is the ability to use the prosthesis on a regular basis and its positive effect on quality of life. This contributes to psychological success as much as the aesthetic and functional success. Assessment of outcomes must also include individual implant success rates and local skin response.

Individual implant success rates

Jacobsson *et al.*¹⁸ proposed the following criteria for success of a craniofacial osseointegrated implant:

1. The unattached implant should be immobile when tested clinically.
2. Soft-tissue reactions around skin-penetrating abutments should be type 0 (reaction-free) or type 1 (slight redness) on the Holgers scale,⁶¹ not demanding treatment in more than 95% of observations.
3. Individual implant performance should be characterized by the absence of persistent and/or irreversible signs and symptoms such as pain, infection, neuropathy, and paresthesia.
4. A success rate of 95% in the mastoid process and 90% in the orbital region in nonirradiated bone tissue at the end of a 5-year observation period should be a minimum criterion for success.

Many studies in the literature have documented implant success rates. A 1992 study¹⁸ showed a success rate of 95% in the mastoid and 72% in the orbital region. It was noted that

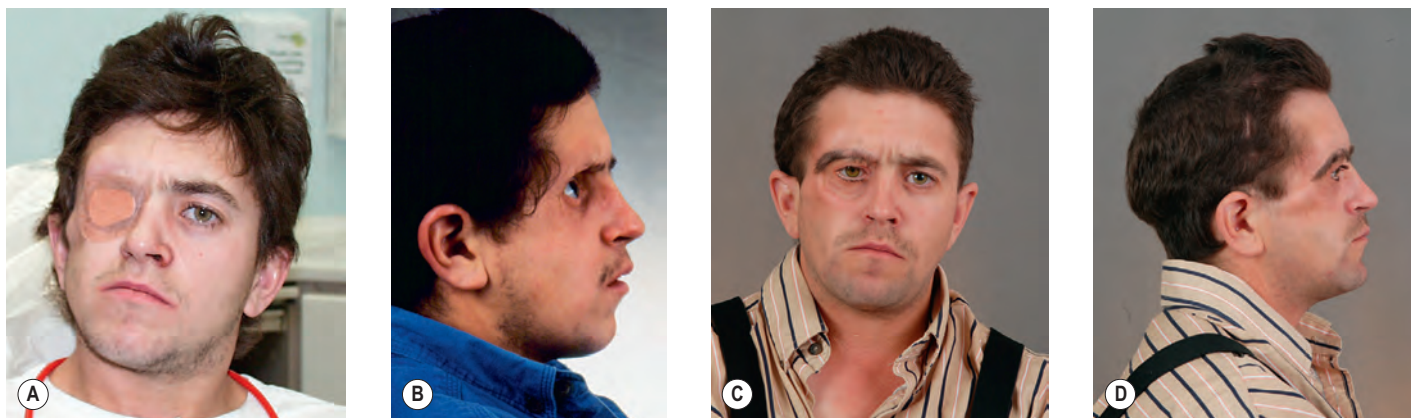


Fig. 31.16 (A–D) As a child this patient underwent enucleation of the right globe and postoperative radiotherapy for a malignant lesion. He was reconstructed with a combination of autogenous and alloplastic techniques. He had an eyebrow reconstruction, onlay cartilage graft to right zygoma, orbital revision, and an osseointegrated orbital prosthesis.

failures in the mastoid occurred within 6 months of insertion whereas failures in the orbital region tended to occur much later. Further evaluation revealed that the success rate in nonirradiated orbits within this group was 92.1% whereas that of the irradiated group was 62.7%. Subsequently, work by Gransström and others has shown that hyperbaric oxygen therapy both before and after implant placement has significantly improved the success rate of craniofacial osseointegrated implants in irradiated bone. In 1994, Granström and colleagues found that, with hyperbaric oxygen therapy, no implant loss had occurred during a 5-year follow-up period in 48 implants placed in irradiated orbital, nasal, and temporal regions.⁴⁷

Skin response

The most common problems are related to the skin response around the percutaneous abutments. Although this does not usually threaten the long-term success of the individual implant, it requires much of both the clinician's and patient's time to overcome this problem. Occasionally, further surgery may be indicated. Tjellström reported that 15% of his patients accounted for 70% of skin reactions.¹⁷ He reported a grading of no skin reaction in approximately 90% of his patients. A factor contributing to adverse skin reaction was adolescence

because of behavior problems and poor compliance with local hygiene (Fig. 31.18).

Prosthetic success

Several studies have been published documenting prosthetic success from a patient's perspective.^{17,59,62,63} In a study from 1990,¹⁷ only 2 of 94 patients were not wearing their prosthesis at the time of assessment. Tolman and Taylor⁶² evaluated patients with nonimplant-retained prostheses, and only 50% considered their prosthesis stable. After these patients had craniofacial implant prosthetic reconstruction, 93% rated their implant-retained prosthesis as stable. Of 30 patients, 19 wore the prosthesis more than 12 hours per day, three wore the prosthesis 8–12 hours per day, three wore the prosthesis 4–8 hours per day, and five wore the prosthesis less than 4 hours per day. Of 30 patients, 24 viewed the prosthesis as an extension of themselves and part of their body image. Westin *et al.* found 95% of their patients wore their prosthesis every day and in most cases more than 10 hours per day.⁶³ In a recent study by Korus *et al.*⁶⁴ of osseointegrated ear prosthetic patients, 90% of patients rated their confidence as good with their prosthesis compared to 16% without, and 100% felt that the prosthesis felt like part of them. In regard to the implant

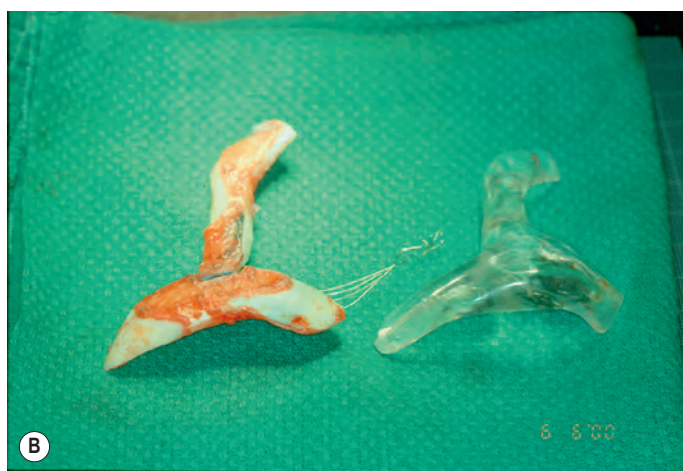
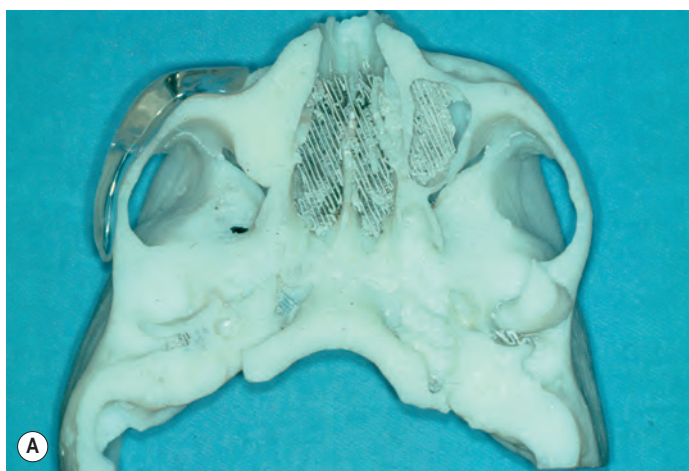


Fig. 31.17 (A,B) Medical modeling technology is used to help construct appropriate cartilage graft and to help with implant placement.



Fig. 31.18 Adverse skin reactions can intermittently be a problem requiring treatment. Lower abutment shows no soft-tissue reaction while upper abutment shows some tissue hypertrophy.

system, 55% felt that they had a skin reaction; however, 83% did not consider their reaction severe. Ultimately most patients were satisfied (97% satisfied, and 74% very satisfied). In all, 94% would ultimately undergo the same procedure again and 97% would recommend it to others.

Conclusion

Craniofacial osseointegration has an important role in the treatment of major head and neck defects. It offers treatment options in many situations where in the past only poor ones existed. Patient satisfaction is very high and they often become strong advocates for this treatment modality. Craniofacial

osseointegrated prosthetic reconstruction adds another floor where the reconstructive elevator can stop.

The future of craniofacial osseointegration includes the development of new implants and implant surfaces to stimulate bone formation and remodeling to improve long-term success. Growth factors, stem cells, and new drugs will help improve success rates in compromised tissues. Further developments using advanced digital technologies such as rapid prototyping,^{65,66} image acquisition technology,⁶⁷ software manipulation systems, and color-matching software,⁶⁸ will make prosthetic reconstruction more accurate, faster, and potentially cheaper. New methods of noninvasive testing will allow better evaluation of implants, and better strategies to prevent implant loss will be devised.⁶⁹ Presently skin does not attach to the percutaneous abutment so the connection is maintained essentially as an open wound. Improved understanding of this soft-tissue interface will allow for more use elsewhere in the body, including the extremities, where contamination is more common.⁷⁰ Combining osseointegration technology with microelectronics could produce movable or sensory prosthetics^{71–74} or some type of seeing orbital prosthesis.⁷⁵ Large titanium implants will secure large-extremity prosthetics better.^{76,77} The future is exciting for a whole field of endeavor that started with the chance observation by P.I. Brånemark of an unusual behavior of a metal in a blood flow study in rabbits!



Bonus images for this chapter can be found online at

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Fig. 31.1 Historical development of osseointegration biotechnology. Through the Brånemark experience, osseointegrated implants have been subjected to over 30 years of scientific scrutiny. Craniofacial applications were first introduced in 1977. EO, extraoral.



Access the complete reference list online at <http://www.expertconsult.com>

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Transplantation in plastic surgery

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SYNOPSIS

- The most important antigens contributing to allograft rejection are the major histocompatibility complex (MHC) antigens.
- The immune system has two main arms that mediate both rejection and tolerance to foreign antigens: the humoral response (B cells and antibodies) and the cell-mediated response (T cells).
- T lymphocytes have a central role in coordinating the immune response, forming the cell-mediated arm of the immune response.
- Acute rejection takes place days to weeks after transplantation and occurs with rapid onset. This T-cell-mediated response is characterized by fever, graft tenderness, and edema, and loss of function. Interstitial lymphocytic infiltration is seen on microscopic examination.
- Chronic rejection is characterized by fibrosis and severe organ dysfunction. This process usually occurs over years.
- Immunosuppressive medications must inhibit the body's ability to reject a transplanted organ, but not at the expense of the defense network against pathogens.
- Despite the use of powerful immunosuppressive medications most transplant patients experience episodes of acute rejection.
- Two major issues in hand transplantation are the need for maintenance immunosuppression and the evaluation of the functional outcomes of the transplants.
- Clinical hand and face transplantation have expanded over the past 5 years but still are limited by the need for chronic immunosuppression and the threat of rejection.

The fields of transplantation and plastic surgery have always been closely linked. In fact, the age of organ allotransplantation in the US began when Joseph E. Murray, a plastic surgeon, transplanted a kidney between identical twin brothers in 1955.¹ Such "reconstructive surgery" using organ allografts was one of the great achievements in 20th-century medicine. Plastic surgeons often reconstruct tissue defects via transplantation of autologous tissue from other regions of the body. Nonvascularized skin, bone, and cartilage grafts alone or in combination with axial and random flaps are common everyday procedures used to reconstruct tissue defects. However,

these surgical techniques all have significant limitations, often require revisions, and leave the patient with a donor site. Advances in the development of skin substitutes (prepared from allogeneic or xenogeneic sources) and the application of frozen bone allografts have shown the possibility of reconstruction without a donor site but their application is limited. Despite advances in plastic and reconstructive surgery, including the refinement of microvascular techniques and delineation of flap vascular anatomy, many complex wounds, especially those on the central face, still remain outside the realm of possibility for restoring both form and function.

The inability to reconstruct missing tissues accurately occurs when the surgeon must deviate from the principle of replacing "like with like" due to a lack of appropriate autologous donor sources. Thus, the function of a severely injured extremity cannot be adequately restored, the appearance of a severely disfigured face cannot be satisfactorily improved, and both the function and appearance of an amputated extremity cannot be reconstructed. Understandably, the inclination toward tissue transplantation has led plastic surgery researchers to look to non-autogenous sources for reconstructive material.²⁻⁴ However, the ability to engineer tissue from single cell sources has yet to yield a technique that can provide the complex tissue constructs needed. One technique with the potential for providing access to complex vascularized tissue constructs without the need for a donor site is through the process of allotransplantation.

The clinical feasibility of vascularized composite allograft (VCA) has been demonstrated by the successful transplantation of over 107 hands and 37 faces worldwide.⁵⁻¹¹ The field of reconstructive transplantation represents a paradigm shift in the arena of reconstructive surgery. The application of these transplants to patients with complex wounds can provide the reconstructive surgeon with the opportunity to reconstruct with the exact tissues lost. However, unlike traditional solid-organ transplants (kidney, liver, and heart) that consist of relatively homogenous parenchymal tissue, the vascularized composite allograft is comprised of multiple heterogeneous tissue types (skin, bone, and muscle). Each of these distinct

tissue types has been shown to exhibit varying degrees of antigenicity, with skin and mucosa the most antigenic.¹² While solid-organ transplantation is the gold standard for the treatment of end-stage organ failure, there has yet to be true consensus on the use and application of vascularized composite allografts.^{13,14} The survival of the hand and face transplants is dependent on the use of chronic immunosuppression and their application is currently limited to experimental institutionally approved protocols. In order for the field of reconstructive transplantation to expand its indications beyond the experimental arena, techniques need to be designed either to significantly reduce or eliminate the need for chronic immunosuppression. The future direction of this field is heavily dependent on the development of innovative approaches to the use of immunosuppressive agents and tolerance induction protocols.

Nomenclature

A graft is nonvascularized tissue (such as skin) that is harvested from its donor bed and transferred to a recipient site. Its survival relies on ingrowth of new vessels from the recipient bed to restore its blood supply. In contrast, a flap involves the transfer of vascularized tissue (such as muscle and skin) via either the preservation of an axial blood vessel or microvascular anastomoses of that vessel to recipient vessels located adjacent to the wound. An autograft is tissue transplanted from one location to another in the same individual. An isograft is transplanted from a genetically identical donor to the recipient, such as transplants between syngeneic mice and human monozygotic twins. An allograft is transplantation of tissues between unrelated individuals of the same species. A xenograft is transplantation between different species.

Transplantation may also be described in terms of the site into which the tissue is transplanted. Orthotopic refers to transplantation into an anatomically similar site; heterotopic refers to transplantation into an anatomic site different from the site of origin.

Transplantation immunology

Major histocompatibility complex

The most important antigens contributing to allograft rejection are the major histocompatibility complex (MHC) antigens. The MHC proteins are encoded in a gene complex on the short arm of chromosome 6 and have different nomenclature between species: human leukocyte antigen (HLA) in humans, swine leukocyte antigen (SLA) in swine, H-2 in mice, and RT1 in rat. MHC genes are expressed in a codominant fashion, with one haplotype, or set of alleles, inherited from each parent.

There are two major classes of MHC genes. Class I MHC genes encode a transmembrane glycoprotein complex with a polymorphic 44-kDa heavy chain consisting of three extracellular domains (α_1 , α_2 , and α_3). The α_1 domain is highly variable and contains sites for antigen binding. The heavy chain is stabilized by noncovalent binding to a lighter chain, referred to as β_2 -microglobulin. There are three distinct genetic loci for the class I antigens in the human: HLA-A, HLA-B, and HLA-C.

Class I antigens are expressed on nearly all nucleated cells and serve as the primary target for cytotoxic (CD8+) T lymphocytes. Class II MHC genes encode two noncovalently bound transmembrane proteins, a 34-kDa α chain and a 29-kDa β chain. There are three class II loci in humans: HLA-DR, HLA-DP, and HLA-DQ.¹⁵ Class II antigens are expressed primarily on vascular endothelium and cells of hematopoietic stem cell origin such as lymphocytes and macrophages.

Both class I and class II molecules have a specific site at which foreign peptide antigens can be presented after they have been processed by the cell.¹⁶⁻¹⁹ Tissue distribution is not the same in all species: humans, dogs, pigs, and monkeys express class II antigens on endothelial cells, whereas rodents and many species do not.²⁰ Matching of HLA-A, HLA-B, and HLA-DR has been found to be an important factor in determining long-term renal allograft survival.²¹

Other transplant antigens

In addition to the MHC antigens, there are three other classes of surface proteins: ABO blood group proteins, minor histocompatibility antigens, and skin-specific antigens.

The blood group antigens are important in clinical transplantation because they are expressed on vascular endothelial cells. Patients with type A or type B blood develop natural antibodies to the other protein, whereas patients with type O blood develop natural antibodies to both type A and type B proteins. Although ABO antigens will not stimulate cell-mediated rejection, a brisk antibody-mediated attack can rapidly lead to graft failure.²²

Minor histocompatibility antigens are peptides of self origin that are not presented by the MHC complexes. Siblings (other than identical twins) with a completely matched MHC profile will still differ with respect to minor antigens because of allelic variation of the genes encoding those proteins. Although minor antigens will stimulate a cell-mediated response, they will not do so in a primary *in vitro* test. Rejection of a graft due to minor antigens alone, therefore, often proceeds at a slower rate.²³

Skin-specific antigens (Sk antigen) are tissue-specific proteins that can cause graft rejection by a cell-mediated response. Consequently, skin is one of the most difficult tissues to which transplantation tolerance can be induced.²⁴

Immunologic rejection cascade

Cells of immune response

A number of cells with varied but interconnected functions participate in the process of graft rejection. They work together to maintain the two main arms of the immune reaction, the humoral response (B cells and antibodies) and the cell-mediated response (T cells).

Macrophages

The macrophage performs the most ancient cellular defense function: phagocytosis. It is of mesenchymal origin and thought to arise from a bone marrow stem cell. It can freely circulate throughout the body, migrate through lymph nodes, or remain stationary within tissues. Kupffer cells are specialized macrophages that reside in the liver. The Langerhans cell is a specialized macrophage that is specific to the skin. The

macrophage expresses class I antigens on its cell surface, and as a highly specialized immune cell, the macrophage also expresses class II MHC molecules.

Beyond simple destruction of cells, the main purpose of the macrophage is to reprocess the breakdown products of ingested cells. These fragments of foreign protein may then be bundled with a new class II antigen molecule, and during the bundling process, fragments of the foreign protein come to reside in the peptide-binding groove of the class II molecule. When the fragment is exteriorized, it faces outward and is easily recognized by the immune system as foreign. This process is known as antigen presentation. Macrophages also secrete important cytokines,^{25,26} such as interleukin-1 (IL-1). This polypeptide can, in a hormonal fashion, stimulate the immunologic function of responding cells. These cells are critical to the presentation of foreign antigen.

Natural killer cells

Another primitive cell derived from the bone marrow stem cell is the lymphocyte (non-T, non-B) called the natural killer (NK) cell. NK cells are thought to be active in the antitumor response.²⁷ They are able to demonstrate spontaneous tumoricidal properties on exposure to tumor cells. This cell does not require recognition of MHC molecules or antigen processing (as do T cells and B cells).²⁸ However, the exact method this cell uses to recognize foreign cells remains unclear. They are able to kill cells by incorporating a lipophilic protein into the target cell membrane, which leads to increased permeability and cell lysis. NK cells also secrete several cytokines, including interferon- γ , interferon- α , and B-cell growth factor. They may also serve to eliminate cells that fail to express normal self-MHC proteins and thereby be self-reactive. Finally, they appear to serve as a barrier to the engraftment of donor bone marrow after non-MHC-matched bone marrow transplantation.²⁹

Granulocyte

The granulocyte plays an important role in immune homeostasis. Named for their histologic staining properties, the three main cell lines are polymorphonuclear cells, eosinophils, and basophils. All of the cell lines are derived from the same bone marrow precursor. As nucleated cells, they all express class I MHC molecules; however, they do not express class II MHC antigens. In addition, these cells express a number of molecules important for their function (including adhesion and interaction with other immune cells) on their cell surface. These white blood cells carry granules of toxic substances (peroxidases) and substances that attract other white blood cells and cellular elements of the coagulation cascade. When stimulated, the granulocyte secretes these granules, initiating local inflammation in a relatively indiscriminate fashion.

B lymphocyte

Named for their site of origin in the chicken, the bursa of Fabricius, these cells play a central role in immune defense. In humans, the bursa equivalent is thought to be the fetal liver or bone marrow. Once these cells are produced, they migrate to the lymph node and spleen and appear to remain in these organs. These cells express class I and II MHC antigens. They also display a variety of B-cell-specific markers, known as B1–B8 (through which the lines of B cells can be identified).

Finally, they display immunoglobulin on their surface. When stimulated, the B lymphocyte differentiates into plasma cells. These smaller cells serve as factories to produce specific antibodies. These soluble antibodies support the humoral arm of the immune response. Through rearrangement of a highly variable genetic region during immune development, antibodies are produced that can bind countless millions of different epitopes.

Immunoglobulin

Antibodies produced by B lymphocytes and plasma cells take the form of immunoglobulins. Immunoglobulins are proteins of unique structure, composed of heavy and light peptide chains. The “root” of the heavy-chain complex is called the constant fragment. The portion of an immunoglobulin molecule where light chains form complexes with heavy chains, at the site at which the antibody will bind to its target, is designated the antibody-binding fragment (Fab). Myriad possibilities exist for antigen to a specific antibody to be made because the Fab moiety is highly variable in its discrete structure. More than 100 genes code for specific segments of the variable portions of the heavy and light chains, leading to millions of potential immunoglobulin specificities.

There are five general immunoglobulin classes: IgM, IgG, IgE, IgA, and IgD. IgM is the first antibody formed after exposure to common microbial antigens, followed by the more durable IgG. IgE is involved in the hypersensitivity reaction by binding to and activating specialized eosinophils (mast cells). IgA is secreted in saliva, tears, and breast milk and thus augments resistance to infection in these fluids. IgD is found on the surface of immature B lymphocytes; its function remains unclear. Immunoglobulins may be soluble or bound to a cell's surface.

The main function of immunoglobulins is to provide opsonization and to activate complement. Opsonization occurs when the Fab fragment of an immunoglobulin binds to its associated antigen, such as an invading organism. Subsequent macrophage and monocyte phagocytosis of the antibody-coated microorganism is then markedly enhanced. Complement fixation occurs when the antibody–antigen complex triggers the complement cascade.

Complement

An antigen–antibody complex may initiate the complement cascade through a classical pathway. Substances such as endotoxin may, without immunoglobulins, initiate the cascade through the alternative pathway. Both pathways converge with the activation of C3. The sequential activation of proteases, which define the complement cascade, results in a tight cluster of proteins known as the membrane attack complex. This complex is able to rupture the membranes of foreign cells. In the normal host, this cascade is kept in check by the regulatory protein C1 inhibitor.

Dendritic cells

These cells are derived from bone marrow stem cell progenitors and are highly specialized antigen-presenting cells. They appear to have little to no effector function. They reside in the intracellular and interstitial space but migrate through the lymphatics and to the spleen when activated. There they present their antigens to T-cell-rich areas.

T lymphocytes

T lymphocytes have a central role in coordinating the immune response, forming the cell-mediated arm of the immune response. The T lymphocyte is named for its site of origin, the thymus, and is one of the central elements of the immune system. T cells derive from fetal stem cells in the thymus and undergo an extensive process of education and deletion before being released into the body. The maturing T cells are selected to recognize self MHC antigens and become tolerant to them. Those cells that demonstrate too high an affinity to self are eliminated by clonal deletion. Failure of this process appears to lead to autoimmunity.

These cells express both class I and class II antigens. In addition to HLA surface markers, lymphocytes also possess cell surface markers that serve to distinguish one subpopulation from another within the same individual. These are all glycoproteins and are described by the common determinant (CD) nomenclature (e.g., CD3).

Three broad classes of T cells are helper T (T_H) cells, cytotoxic T cells, and suppressor T cells. All T cells express CD3 on the cell surface. Cytotoxic T cells (cells that effect target cell killing) express CD8. Suppressor T cells that can buffer and down-regulate the immune response also express CD8.^{30,31} T_H cell, however, expresses CD4 and serves to amplify the immune response through its interaction with other cells and secretion of critical cytokines. Each T cell expresses a T-cell receptor (TCR) capable of binding antigen. The TCR, a 90-kDa heterodimer composed of an α chain encoded on chromosome 14 and a β chain encoded on chromosome 7, is located close to the CD3 antigen and the CD28 antigen. The TCR is relatively flat and possesses an outward-facing surface. This "antigen recognition platform" is the critical interface for foreign peptide in the binding groove. As with B-cell development, T cells undergo rearrangement of genes coding for a hypervariable region on the receptor proteins. This allows a body's population of T cells to respond to a nearly limitless array of foreign antigens, with each individual T cell capable of binding one specific antigen.

T-cell binding and activation

Although the TCR is capable of binding antigen, it will not recognize the target molecule by itself.³² The TCR can bind antigen only if it has been processed and presented by an antigen-presenting cell together with an MHC molecule; thus, it recognizes the MHC together with the target antigen. This limitation of binding is referred to as MHC restriction. CD4 (helper) T cells can only bind antigen presented with MHC class II molecules; CD8 (cytotoxic) T cells recognize antigen along with MHC class I proteins. The T_H cell is most critical to the immune response because its activation results in the production of cytokines that are necessary for the function of many other immune cells. Binding of a CD4 cell to an antigen-presenting cell that expresses target antigen together with MHC class II molecules initiates a predictable cycle of intercellular communication. The antigen-presenting cell is stimulated to produce the cytokine IL-1, a powerful chemoattractant, a primary mediator in the acute-phase reaction, and a potent activator of lymphoid cells. The T cell, in turn, secretes IL-2, which is a required stimulant for differentiation and proliferation of T cells. The IL-2 produced by the bound T cell has autocrine function by binding to newly expressed self IL-2

receptors. Secreted IL-2 also has paracrine function that affects other T cells in the region, such as CD8 cells, which require IL-2 for activation but do not produce it themselves. As CD4 cells become further activated, they secrete IL-4 and IL-5, which stimulate the maturation and proliferation of B lymphocytes. Furthermore, there is evidence that two subsets of CD4 cells, T_H1 and T_H2 , function to enhance alloreactivity and stimulate antibody production by B cells, respectively. With such a central role by CD4 cells in cell signaling, it is easy to understand the severely compromised immune response from the loss of host CD4 cell function secondary to human immunodeficiency virus infection.³³⁻³⁶

Antigen recognition and graft rejection

In the case of allograft tissue, foreign antigens would be recognized by host T cells after being processed by host antigen-presenting cells and presented in the context of self MHC. This is termed indirect presentation. In addition, host T cells can directly recognize donor MHC on donor antigen-presenting cells, termed direct presentation. This mechanism helps explain the more vigorous response to allograft tissue than to foreign peptides alone.³⁷

Clinically, rejection of allograft tissue can proceed at different levels of intensity for different tissues. The common component for rejection of any graft is inflammation. This may be manifested as a loss of graft function with local or systemic signs of inflammation. Several distinct clinical syndromes of graft rejection with different time courses have been noted. These syndromes differ with regard to the underlying primary immunologic process.

Hyperacute rejection occurs almost immediately after perfusion of the allograft with host blood. It is the result of preformed antibodies to either ABO blood group proteins or donor MHC molecules enacting a rapid attack on the donor tissue. Complement activation results in destruction of vascular endothelial cells and induces rapid thrombosis of vessels as well as an amplification of the inflammatory signal. Standard screening before transplantation should detect preformed antibodies, making hyperacute rejection a rare clinical entity. Many mammals possess preformed antibodies to other species that stand as a major obstacle to xenotransplantation.³⁸

Acute rejection takes place days to weeks after transplantation and occurs with rapid onset. This T-cell-mediated response is characterized by fever, graft tenderness, and edema, and loss of function. Interstitial lymphocytic infiltration is seen on microscopic examination. In addition, severe forms of acute rejection may include a humoral attack on the graft, resulting in a vasculitis.³⁹

Chronic rejection is an indolent process occurring months to years after transplantation. It is characterized by a progressive loss of tissue architecture with fibrosis and mononuclear cell infiltration. The etiology of chronic rejection is not well understood and may be multifactorial. The process may be slowed because of immunosuppression. It also may result from the cumulative effect of damage to the graft from ischemia during transplantation, graft infection, or drug toxicity.

Inflammatory mediators in transplantation

In addition to the direct cellular interaction observed during an immune response there are also multiple inflammatory mediators involved in immune activation and regulation.

These include cell adhesion molecules (CAM), cytokines, and chemokines that are all critical to a functioning immune system. Cytokines are transient regulatory proteins that a wide variety of cells can produce in response to stimulation. These proteins can act locally by binding to a cell from the same cell line (autocrine) or to the target cell in the vicinity (paracrine).⁴⁰ The cytokines are divided into proinflammatory cytokines (IL-1 α , IL-1 β , IL-6; tumor necrosis factors: TNF- α , TNF- β), cytokines involved in T-cell differentiation (IL-2, IL-4, IL-5, IL-10, IL-12, IL-13, and interferon- γ), and cytokines of immunoregulatory function belonging to the transforming growth factor- β family, which primarily promotes wound healing and fibrosis.⁴⁰

Chemokines are a subset of cytokines that are currently defined as small chemotactic cytokines. Chemokines, which are constitutively expressed, are involved in homeostatic lymphocyte trafficking to the lymphoid organs and bind to the cellular component by a specific chemokine receptor. The main role of proinflammatory chemokines (macrophage inflammatory protein-1 α (MIP-1 α), MIP-1 β , monocyte chemoattractant protein-1 (MCP-1), and RANTES) is to attract neutrophils to an inflammatory site and trigger T lymphocytes to elicit an additional inflammatory response.⁴¹ In humans, CCR1-positive cells increase in the peripheral blood of renal allograft recipients before acute rejection.⁴² In addition, CCR1 mRNA was found to be expressed in cells derived from biopsies from renal allografts.⁴³ Ruster *et al.* described an increased number of CCR1-positive cells in glomeruli during rejection.⁴⁴ Mayer *et al.* reported that the mRNA expression of CCR1 was associated with the decrease of renal function in allografts with an acute rejection episode.⁴⁵ Thus, it is clear that chemokines play an important role in allograft rejection and interruption of these interactions could have an impact on allograft survival.

CAMs play a role in leukocyte migration from the circulation to tissues. Three types of CAM are involved in the transmigration process: selectins (L-, E-, and P-selectins) mediating the rolling of leukocytes along the vascular endothelium, integrins (intercellular adhesion molecule-1 (ICAM-1), vascular CAM-1 (VCAM-1), mucosal addressin cellular adhesion molecule-1 (MAd CAM-1)) leading to leukocyte adhesion to the endothelium, and finally immunoglobulin superfamily platelet endothelial CAM-1 (PECAM-1), responsible for transmigration of leukocytes.⁴⁶ The complex specific migration of leukocytes to the target tissue requires a coordinated process of proinflammatory mediators. Proinflammatory cytokines, IL-1 α and TNF- α , may induce expression of proinflammatory chemokines. Chemokines play a major role in the activation of integrins needed for adhesion of rolling leukocytes to the vessel endothelium, and this process leads to leukocyte transmigration to the surrounding tissue, initiating the inflammatory process.

Immunologic screening

Methods are available to predict the compatibility of donor tissue to a particular recipient. The greatest value of these clinical tests is to exclude recipients who would be expected to manifest a hyperacute rejection to a specific donor organ.

Blood group typing is an important first step in determining transplant compatibility. An ABO mismatch will result in certain failure because of preformed antibodies.⁴⁷ Although it

is possible to transplant type O donor tissue into type A or type B recipients, the limited supply of donor organs in the US makes this practice uncommon.

HLA typing is used to match organs with potential recipients. Serologic methods are employed to type HLA-A, HLA-B, and HLA-DR. A heterozygous individual with a complete match at all these loci is referred to as a six-antigen match. For renal allografts, HLA matching has been shown to affect graft survival. Kidneys transplanted from HLA-identical siblings have a 3-year success rate that well exceeds 90%, whereas parent-to-child grafts have an 82% survival. Cadaveric kidney grafts have a 70% 3-year survival rate.⁴⁸ MHC class II matching has been found to be more important than class I matching for renal transplantation; the reverse appears to be true for liver transplantation. This would suggest differences in mechanisms of graft rejection for different tissues.⁴⁹ Serologic tissue typing has certain limitations. An HLA antigen can be identified only if it is being searched for with a specific antibody. For example, if only a single HLA-DR phenotype is identified in donor tissue, the individual could be either homozygous for that allele or heterozygous with an unrecognized HLA-DR antigen. This method of testing fails to type the other class II antigens, HLA-DP and HLA-DQ.

Crossmatching is a test that detects the presence of preformed donor-specific antibodies in the serum of a particular recipient. It represents the final definitive screening measure before transplantation. In this lymphocytotoxicity assay, donor lymphocytes are incubated with recipient serum and complement. Cell viability is then assessed by a dye exclusion technique. A positive crossmatch, indicated by lysis of the donor lymphocytes, suggests that a hyperacute reaction is likely to occur. One pitfall of this test, however, is that organ-specific antibodies may be missed if those antigens are not expressed on the lymphocytes being evaluated.

Antibody screening is another modality used in clinical transplantation. Serum from prospective transplant recipients is routinely tested in a lymphocytotoxicity assay against a panel of cells from different donors with known HLA antigens. The percentage of panel cells lysed reflects the degree of panel-reactive antibody (PRA), demonstrating HLA antibodies in an individual's serum. A high PRA suggests that a patient is unlikely to have a negative crossmatch. This information is used in determining organ allocation when the tissue must be transplanted quickly. Individuals are likely to have a high PRA if they have been sensitized by previous transplantation, pregnancy, or blood transfusions.

Current immunosuppression for VCA

The multiple pathways and mechanisms employed by the immune system to defend the body against both extracellular and intracellular pathogens have presented a significant barrier to the survival of transplanted allografts. Immunosuppressive medications must inhibit the body's ability to reject a transplanted organ, but not at the expense of the defense network against pathogens. The use of several immunosuppressive agents has allowed the inhibition of the immune system that maximizes the protection of the allograft with the least cost to the body's overall ability to fight infection and tumors (Table 32.1).

Table 32.1 Antibody-mediated drugs

Agent	Mechanism	Action	Side-effects
Antilymphocyte			
Antilymphocyte globulin	Antibodies directed against antigens on lymphocytes	Promotes T-cell clearance through complement-mediated lysis	Thrombocytopenia, leukopenia, increased risk of viral reactivation, serum reaction
Antithymocyte globulin	Antibodies directed against antigens on thymocytes	Promotes T-cell clearance through complement-mediated lysis	Thrombocytopenia, leukopenia, increased risk of viral reactivation, serum reaction
Alemtuzumab	Antibody against CD52	Eliminates T cells by antibody-dependent cellular cytotoxicity	Thrombocytopenia, leukopenia, increased risk of viral reactivation, serum reaction
OKT3	Murine monoclonal antibody directed against the CD3 subunit on human T cells	Eliminates T cells by the reticuloendothelial system; blocks cytotoxic activity of activated T cells	Significant cytokine syndrome, reactivation of viruses, post-transplantation lymphoproliferative disease
Anti-IL-2			
Daclizumab, basiliximab	Blocks binding to CD25 (high-affinity chain of IL-2 receptor)	Limits T-cell expansion; acts only on activated cells	None
CTLA-4 Ig			
Belatacept	Selective T-cell costimulation blocker binds to CD80 and CD86 receptors on antigen-presenting cells (APC)	Blocks the required CD28-mediated interaction between APCs and T cells needed to activate T lymphocytes.	Post-transplant lymphoproliferative disorder, other malignancies, and serious infections. Increased risk for developing post-transplant lymphoproliferative disorder, predominantly involving the CNS. Recipients without immunity to Epstein–Barr virus are at a particularly increased risk
IL-2, interleukin-2.			

In all of the transplanted organs including hand and face transplants, it appears that it is central to prevent allograft recognition during the peritransplantation period. This is currently achieved through so-called induction protocols. Several agents are currently used to protect the transplant during that period of cytokine excess observed after surgery (Table 32.2). After the induction agents are used, “maintenance” medications are used to maintain the transplant. Finally, when ongoing rejection occurs, it is often necessary to use “rescue” agents to stop ongoing rejection and salvage a transplant that would otherwise be lost.

Corticosteroids

These agents remain a central tool for both the prevention and treatment of allograft rejection. Whereas steroids are not effective as solitary agents to prevent rejection, they have been shown to improve graft survival in combination with other agents. When used at high doses, they can also treat ongoing acute cellular rejection. Despite these uses, steroids also contribute to the morbidity associated with modern immunosuppression.

Glucocorticosteroids bind to an intracellular receptor after nonspecific uptake in the cytoplasm. The receptor–ligand complex then enters the nucleus, where it acts as a DNA-binding protein and increases the transcription of several genes.⁵⁰ The most important gene is thought to be *IκBα*, which binds to and prevents the function of NF-κB (a key proinflammatory cytokine that is an important transcription factor for

T-cell activation). Steroids block the production of IL-1 and TNF-α by antigen-presenting cells. They also block interferon-γ production by T cells and migration and lysosomal enzyme release by neutrophils. Steroids also mute the up-regulation of the MHC and, through their diminution of the inflammatory responses, decrease the degree of costimulation in the environment. Steroids do not have an impact on the production of antibody.

Antiproliferative agents

Azathioprine

This was the first immunosuppressive agent employed in transplantation and is now largely a historical transplant medication. Azathioprine undergoes conversion in the liver to 6-mercaptopurine and then to 6-thioinosine monophosphate. These derivatives inhibit DNA synthesis by alkylating DNA precursors and inducing chromosome breaks through interference with DNA repair mechanisms. In addition, they inhibit the conversion of inosine monophosphate (IMP) to adenosine monophosphate and guanosine monophosphate (GMP), which depletes the cell of adenosine. The effects of azathioprine are nonspecific, and it acts not only on dividing T cells but on all rapidly dividing cells. The primary toxic effect is on the bone marrow, gut, and liver cells. Azathioprine is ineffective as a single agent and cannot be used as a rescue agent. It has been used for maintenance when it is given in combination with steroids and a calcineurin inhibitor.

Table 32.2 Immunosuppressive drugs

Agent	Mechanism	Action	Side-effects
Calcineurin inhibitors			
Cyclosporine	Binds to cyclophilin, blocks the NF-AT transcription factor, inhibits production of IL-2, and promotes production of TGF- β	Prevents cytokine transcription and arrests T-cell activation	Nephrotoxicity, hypertension, neurotoxicity
Tacrolimus (FK506)	Binds to FK-binding protein, blocks the NF-AT transcription factor, inhibits production of IL-2, and promotes production of TGF- β	Prevents cytokine transcription and arrests T-cell activation	Nephrotoxicity, neurotoxicity, diabetogenicity
Antiproliferative agents			
Azathioprine (Imuran)	Inhibits DNA synthesis, interferes with DNA repair mechanisms, and inhibits conversion of IMP to AMP and GMP	Blocks the proliferative response (T and B cells)	Bone marrow suppression, hepatotoxicity
Mycophenolate mofetil	Noncompetitive, reversible inhibitor of IMP dehydrogenase; interrupts production of GTP and dGTP; prevents critical step in RNA and DNA synthesis	Blocks the proliferative response (T and B cells), inhibits antibody formation, and prevents clonal expansion of cytotoxic T cells	Gastrointestinal toxicity, bone marrow suppression
Corticosteroids			
Corticosteroids	Binds to intracellular receptor, increases transcription of gene for I κ B α , and prevents the transcription of NF- κ B (a key activator of proinflammatory cytokines)	Blocks IL-1 and TNF- α production by antigen-presenting cells, blocks up-regulation of the MHC, inhibits production of interferon- γ by T cells and lysosomal enzymes and migration by polymorphonuclear cells	Osteonecrosis, osteoporosis, growth suppression, glucose intolerance, hypertension, central nervous system effects
Macrolide inhibitors			
Sirolimus (rapamycin)	Binds to FK-binding protein, impairs signal transduction by the IL-2 receptor, and arrests the cell cycle of lymphocytes	Interrupts T-cell activation pathway	Hypertriglyceridemia, bone marrow suppression
AMP, adenosine monophosphate; dGTP, deoxyguanosine triphosphate; GMP, guanosine monophosphate; GTP, guanosine triphosphate; IL-2, interleukin-2; IMP, inosine monophosphate; TNF- α , tumor necrosis factor- α ; MHC, major histocompatibility complex; TGF- β , transforming growth factor- β ;			

Mycophenolate mofetil

Mycophenolate mofetil (MMF), which was approved for use after allograft transplantation in 1995, acts through noncompetitive, reversible inhibition of IMP dehydrogenase.⁵¹ This modification improves the bioavailability of mycophenolic acid. Physiologic purine metabolism requires that GMP be synthesized for the subsequent production of guanosine triphosphate (GTP) and deoxyguanosine triphosphate (dGTP). GTP is required for RNA synthesis and dGTP for DNA synthesis. GMP is formed from IMP by IMP dehydrogenase. MMF prevents a critical step in both RNA and DNA synthesis. However, MMF does not affect the “salvage pathway” for GMP production that is present in most cells. This pathway is not present in lymphocytes, and MMF exploits this difference and spares most other cells in the body, including neutrophils. MMF blocks the proliferative response in both T and B cells, inhibits antibody formation, and prevents clonal expansion of cytotoxic T cells.

MMF decreases biopsy-proven rejection and the need for antilymphocyte agents in rescue therapy compared with azathioprine.^{52–54} MMF has replaced azathioprine in clinical transplantation. However, MMF cannot be used as a sole immunosuppressive agent and must be paired with either

steroids or, more commonly, calcineurin inhibitors (tacrolimus and cyclosporine).

Calcineurin inhibitors

Cyclosporine

Cyclosporine is a cyclic endecapeptide that was isolated from the fungus *Tolypocladium inflatum gams* in 1972.^{55,56} This drug acts as a T-cell-specific immunosuppressant, and its mechanism of action is primarily through its ability to bind to the cytoplasmic protein cyclophilin.⁵⁵ The cyclosporine–cyclophilin complex forms a high-affinity bond with calcineurin–calmodulin complex and blocks the calcium-dependent phosphorylation and activation of NF-AT. The interference with NF-AT prevents the subsequent transcription of the gene encoding IL-2. This process also interrupts other genes critical for T-cell activation. In addition, cyclosporine increases transforming growth factor- β transcription, which appears to down-regulate T-cell activation further, decrease blood flow to the area, and activate pathways critical to wound healing.^{56,57}

The effect of cyclosporine is reversible because it blocks TCR signal transduction but does not inhibit costimulatory signals.³⁸ If the drug is withdrawn, the T cell is not anergic but is again capable of mounting an attack on its target. The effects of cyclosporine can be overcome with the exogenous administration of IL-2. This may explain why cyclosporine is not effective once rejection is ongoing; it is only useful as a maintenance agent and is ineffective as a rescue agent.

Cyclosporine also has significant toxicity associated with its administration. It has significant vasoconstrictor effect (mediated by transforming growth factor- β) on the proximal renal arterioles and this decreases renal blood flow by 30%. Its effects on the kidney can promote fibrosis and hyperkalemia and may interfere with the resolution of acute tubular necrosis. The drug also has neurologic side effects, such as tremors, paresthesias, headache, depression, confusion, and seizures. It may also cause hypertrichosis and gingival hyperplasia. The use of cyclosporine in solid-organ transplantation protocols has largely been replaced by tacrolimus.

Tacrolimus

Tacrolimus (FK506), a macrolide produced by *Streptomyces tsukubaensis*, was discovered in 1986. Tacrolimus, like cyclosporine, blocks the effects of NF-AT, prevents cytokine transcription, and arrests T-cell activation. The intracellular target is an immunophilin protein distinct from cyclophilin known as FK-binding protein.^{58,59} The effect is additive to that of cyclosporine, and these drugs cannot be given together because of the prohibitive toxicity. Tacrolimus also increases the transcription of transforming growth factor- β and thus shares both the beneficial and toxic effects seen in the administration of cyclosporine. It is, however, 100 times more potent in its inhibition of the production of IL-2 and interferon- γ . The renal side effects are similar to those with cyclosporine. It has more pronounced neurologic side effects and a diabetogenic effect. The cosmetic side-effects are less than those with cyclosporine. This drug has been proved to be effective as a maintenance drug for both liver and kidney transplantation. It has only minimal use as a rescue agent.⁶⁰

A topical preparation of tacrolimus has recently been developed and approved for use in atopic dermatitis. Its mechanism of action and local route of administration render it an attractive therapeutic alternative for the treatment of various autoimmune dermatologic conditions and could be of potential use in CTA. It has also been widely used in clinical hand and face transplant immunosuppressive protocols for both maintenance and treatment of rejection.⁵ There has also been some evidence that it can be used in graft-versus-host disease (GvHD).⁶¹ The mechanism by which topical tacrolimus may be effective in GvHD is the suppression of local cytokine secretion such as IL-2, interferon-gamma, and TNF- α in the skin.⁶² The only adverse events reported in its dermatologic applications have been local irritation, pruritus, erythema, and burning.^{63,64} The majority of these symptoms are reported to occur when initiating treatment and systemic effects have not been observed.

Rapamycin

Rapamycin is a macrolide antibiotic derived from *Streptomyces hygroscopicus* and is structurally similar to tacrolimus.^{65,66} However, they antagonize each other's biologic activity. Both

of the drugs bind to the same FK-binding protein, but rapamycin does not affect the calcineurin activity.^{67,68} Instead, the interaction of rapamycin and FK-binding protein complex impairs signal transduction by the IL-2 receptor through its interaction with a cytoplasmic protein (RAFT-1). In doing so, the p70 S6 kinase cascade is interrupted and T cells are prevented from entering into the S phase of cell division.⁶⁹ Thus, rapamycin is able to interrupt T-cell activation and proliferation, even in the presence of IL-2.⁷⁰ Other receptors that are affected are IL-4, IL-6, and platelet-derived growth factor.

Rapamycin has been shown to prolong allograft survival in multiple animal models and is being used in several drug clinical regimens.⁷¹ The drug is most commonly used after the peritransplant period to replace tacrolimus.⁷² It has also been applied to the experimental human hand transplantation patients who have experienced renal toxicity secondary to tacrolimus.⁷³ This drug has little to no nephrotoxicity. It does, however, demonstrate some bone marrow toxicity and has been observed to cause hypertriglyceridemia. Finally, it appears to interrupt the process of wound healing and caution should be applied before using it immediately after surgery.

Antilymphocyte preparations

Antilymphocyte/antithymocyte globulin

Antilymphocyte globulin (ATG) is produced by inoculation of heterologous species with human lymphocytes, collection of the plasma, and then purification of the IgG fraction. The result is a polyclonal antibody preparation that contains antibodies against many of the antigens on human lymphocytes. When thymocytes are used as the inoculum instead of lymphocytes, the product is known as ATG. The most common ones employed in transplantation are made in the horse (ATGAM, Pharmacia & Upjohn, Kalamazoo, MI) and in the rabbit (ATG (Thymoglobulin), SangStat Medical, Fremont, CA).

The mechanism behind the effectiveness of these drugs is through the coating of the T cells by the antibodies.^{74,75} These coated T cells are then eliminated by complement-mediated lysis and opsonin-induced phagocytosis. The mere presence of the antibodies on the surface of the T cell reduces its ability to express an effective TCR signal. The overall impact of the antibodies is functionally to remove the primary effector cells required for acute rejection after transplantation.

These drugs have been employed as induction agents at the time of transplantation to reduce the possibility that T-cell-mediated antigen recognition will occur when the graft is in its most vulnerable state. These drugs are also used as rescue agents, and their effectiveness is based solely on their ability to destroy cytotoxic T cells. Most of the side effects are due to the drug's heterologous origin and the fact that it can also bind to other cells. Therefore, one can observe thrombocytopenia, anemia, and leukopenia. The most common reaction is a cytokine release syndrome. Chills and fevers occur in up to 20% of patients. A rash consisting of raised erythematous wheals on the trunk and neck is seen in 15% of patients. The use of antilymphocyte drugs has been associated with the reactivation of viral disease.

The extent of peripheral lymphocyte depletion in the blood appears to be dose-dependent. Although these agents

preferentially bind to T cells, they may also bind to B cells, dendritic cells, and other nonlymphoid cell lines, especially at high doses. In fact, two pilot studies have demonstrated that high-dose ATG induction can facilitate monotherapy maintenance immunosuppression in selected patients, with graft and patient survival comparable to the current standard.^{76,77} Treatment with ATG has been shown to be associated with both short- and long-term changes in T-cell populations, generating altered homeostasis characterized by expansion of specific T-cell subsets that have been shown to exhibit regulatory suppressor functions. The use of ATG induction has been demonstrated to result in a lower incidence of acute rejection and improved graft survival during the first year after transplantation. However, as has been observed with most induction agents, patient and graft survival after 20-year follow-up were not affected.⁷⁸

OKT3

This is a murine monoclonal antibody that is directed against the signal transduction subunit on human T cells (CD3). OKT3 is thought to bind to the CD3 subunit found on all mature T cells and results in the internalization of the receptor, thus preventing antigen recognition and TCR signal transduction.^{79,80} In addition, T-cell opsonization and clearance by the reticuloendothelial system occur. After the administration of OKT3, there is a rapid decrease in the circulating CD3+ T cells. There is little or no effect on those cells in the spleen and lymph nodes or thymus. After several days, there is a return to T cells that are CD4+ and CD8+ but that do not express CD3. These “blind” T cells remain incapable of binding to antigen and interfere with the process of antigen recognition and generation of cytotoxic T cells. Finally, OKT3 blocks the cytotoxic activity of already activated T cells by an inappropriate degranulation when the CD3 is bound by OKT3. This mechanism is central to its effectiveness but also to one of its most significant side effects.

The administration of OKT3 can lead to a profound systemic cytokine response that can result in hypotension, pulmonary edema, and a fatal cardiac myodepression. In about 2% of patients, this syndrome is manifested as an aseptic meningeal inflammation. Methylprednisolone must be administered before the delivery of OKT3 to blunt this adverse reaction. This syndrome abates with subsequent doses. OKT3 has been used as a rescue agent to treat acute renal allograft rejection. OKT3 has also been employed as an induction agent. The drug is superior to steroids in halting ongoing rejection. However, it has also been shown to cause a high viral reactivation rate for cytomegalovirus, Epstein-Barr virus, and other viruses. It has been associated with high rates of post-transplantation lymphoproliferative disease. Due to its association with these significant complications, its use is extremely limited now. This is especially true after the release of newer induction agents such as alemtuzumab and maintenance drugs such as rapamycin.

Anti-IL-2

Two monoclonal antibodies have become available for use in renal transplantation and have also been employed in some hand transplantations. Both of these agents (daclizumab and basiliximab) are directed against CD25, the high-affinity chain

of IL-2 receptor.^{81,82} These agents were designed to have the same indications for treatment as ATG and OKT3, without the significant side effects of those agents.

The high-affinity chain on the IL-2 receptor is required for T-cell expansion and targeting. This receptor offers the advantage that the CD25 receptor is present only on those active T cells. Theoretically, this agent should affect only those cells that have been activated against a new allograft. This agent is also useful in that it does not lead to the activation of the T cell and therefore potential cytokine release, as is seen with OKT3. These agents have also had several of the murine portions of the molecule replaced with human IgG, thus eliminating much of the nonspecific reactions observed in the heterogeneous antibodies. These agents can be used in the induction phase, but because IL-2 is needed only in the initial activation of T cells, it does not appear to be useful to stop ongoing rejection. Early studies of use as induction agents demonstrated a lower incidence of acute rejection but no long-term graft prolongation in both cardiac and renal allografts.⁸³

Currently it is used as induction therapy with two doses (day 0 and day 4) as part of double- or triple-immunotherapy regimens in adult renal transplant recipients and appears to reduce acute rejection episodes without increasing the incidence of biopsy-proven acute rejection than alemtuzumab induction. Basiliximab is generally associated with a tolerability profile that is similar to that reported with placebo, and better than that reported with ATG.⁸⁴ The drug does appear to allow for reduced dosage of corticosteroids or calcineurin inhibitors, while maintaining adequate immunosuppression, thereby reducing the potential for adverse effects associated with these co-administered agents. However, its use as an induction agent is usually limited to those patients who cannot tolerate either alemtuzumab or ATG.

Alemtuzumab

Alemtuzumab is an anti-CD52 antibody that has enjoyed increased use in solid-organ transplantation as a lympho-depleting induction agent. CD52 is expressed on most T and B lymphocytes, NK cells, and monocytes. Alemtuzumab profoundly depletes T cells from peripheral blood for several months with a somewhat reduced effect on B cells, NK cells, and monocytes (in descending order).⁸⁵⁻⁸⁹ It has very minimal effect on CD34+ hematopoietic stem cells. The initial enthusiasm for its application in solid-organ transplantation was based on research by Calne *et al.*, where 33 kidney recipients were treated with alemtuzumab in combination with low-dose cyclosporine. These patients were then compared to the unit's historical control of patients on standard triple therapy.^{90,91} The 5-year survival of these two groups was similar and this finding led to the initial suggestion that the use of this agent could lead to “prope” tolerance (graft acceptance with reduced immunosuppression).⁹¹ However, later attempts to use the drug alone or in combination with deoxyspergualin led to 100% acute rejection, demonstrating that the drug itself was not tolerogenic. This may be due to the lack of CD52 expression on plasma cells and poor effect on memory T cells. Alemtuzumab combined with a single agent for maintenance (low-dose calcineurin inhibitors) demonstrated safety and efficacy, but has an unacceptably high rate (28%) of early cellular and humoral acute rejection. The drug is currently used as an induction agent with tacrolimus and MMF. Several

groups have used it as their induction agent of choice in clinical hand transplants. However, its use is limited due to a lack of availability and limited production.

Belatacept (CTLA-4 Ig)

Belatacept, a fusion protein between a modified extracellular domain of CD152 and human IgG1, is approved for use as a replacement for tacrolimus in kidney transplantation. Belatacept is a selective costimulation blocker and is clinically indicated as a CNI inhibitor substitute with mycophenolate mofetil and steroids after renal transplantation. Studies in murine models have shown synergy between costimulation blockade and mTOR inhibitors such as rapamycin. Studies in nonhuman primates have demonstrated that the combination of belatacept and sirolimus prolongs renal and islet allograft survival. Clinically, phase III trials have shown supremacy of belatacept in the conservation of renal function and other adverse events compared to CNIs. Its clinical use in VCA transplantation has been limited. There have been reports of transitioning patients from tacrolimus to belatacept to preserve renal function. Cendales reported a case of a hand transplant recipient who developed recurrent acute rejection with alloantibody formation and concomitant calcineurin inhibitor nephrotoxicity that appeared to resolve upon conversion from a maintenance regimen of tacrolimus, mycophenolate mofetil and steroids to belatacept and sirolimus.⁹² There have also been reports from the Austrian group that in three out of four patients the addition of belatacept allowed them to lower the dose of tacrolimus in their drug regimen.

Immunologic tolerance

The ultimate goal of transplantation science is to make genetically disparate organs or tissues be accepted and regarded as self. This would make chronic immunosuppression obsolete and allow the recipient to maintain an intact immune system to protect against infections and malignant neoplasms. As true immunologic tolerance would be “functionally complete”, the life expectancy of the organ would not be limited by chronic rejection. This section provides an overview of the various mechanisms of T- and B-cell tolerance and what is known about their role in models of transplant tolerance.

In the transplantation setting, it appears that T-cell-dependent immune responses are regarded as the primary cause of graft rejection. Thus, T-cell tolerance is important to the generation of tolerance to organ allografts. Mechanisms of T- and B-cell tolerance can be divided into three broad categories: clonal deletion, anergy, and suppression. Clonal deletion is the process whereby T cells with particular antigen specificity are eliminated from the repertoire. Anergy is a state in which T cells can recognize a foreign antigen but are functionally inactive and do not generate an immune response. Suppression implies the presence of cells that are capable of actively preventing other T cells from generating a response. The current thought on the mechanism of suppression is based, in part, on direct action of T-regulatory cells (T regs). These mechanisms are not mutually exclusive, and the establishment of tolerance may depend on more than one of these pathways. The application of these

mechanisms for the induction of tolerance could offer the future plastic and reconstructive surgeon the transplantation of foreign tissues without the need for prolonged immunosuppression.

Clonal deletion

Clonal deletion is the process in which T cells that express a TCR specific for a certain antigen are eliminated. The deletion of these cells can occur in the thymus (central deletion) or extrathymically in the peripheral tissues (peripheral deletion). The thymus is the major site for the generation of immunocompetent T lymphocytes. T-cell progenitors migrate from the bone marrow to the thymus, where they undergo a well-defined pathway of maturation. Once the T cells express their respective TCRs, they then undergo a process of selection. During this process, cells with low-affinity TCRs are not stimulated to progress; this is called positive selection. T cells in the thymus with a high affinity for self antigen are eliminated by a process called negative selection. When this process is complete, the remaining T cells should be able to recognize self and mount a response only when they encounter foreign antigen. Extrathymic clonal deletion has been described in several experimental models using exogenous antigens⁹³⁻⁹⁵ as well as self antigens,⁹⁶⁻⁹⁸ demonstrating that elimination of self-reactive antigens can occur after maturation in the thymus. This mechanism may ensure tolerance to self antigens not expressed in the thymus. Several strategies attempt to influence this process.

The acceptance or tolerance of one's own tissues first develops *in utero* along with an immunologic ability to recognize foreign tissue. This phenomenon was successfully exploited by Medawar⁹⁹ in his original experiments in which strain-specific neonatal rodents were injected with donor cells and went on to accept skin allografts. The production of the tolerant state in an adult can be achieved experimentally by various methods. A combination of total body irradiation to remove mature recipient T cells followed by donor bone marrow infusion before transplantation induces a state of chimerism. (The term *chimera* is derived from the Greek mythological figure composed of parts from different animals.) The chimeric host then develops an immune system that is tolerant of both donor and self antigens. A further refinement is the use of total lymphoid irradiation; the marrow cavities of long bones are protected during irradiation, thus producing a state of mixed chimerism.¹⁰⁰ These animals have gone on to accept donor hearts and kidney allografts. Another method of achieving transplant tolerance involves intrathymic injection of donor cells. These cells survive in the immunologically “privileged” thymus and cause production of maturing T cells that are tolerant of the donor alloantigen.^{101,102} All of these methods take advantage of the central mechanism of tolerance induction and rely on the phenomenon of clonal deletion.

Anergy

For a T cell to become optimally activated, it requires a second, independent costimulatory signal in addition to the primary signal that is generated through contact between the TCR and the MHC. When T cells are stimulated in the absence of these signals, they can become functionally nonresponsive to repeated stimulation with antigen and are termed anergic.¹⁰³

Two major costimulatory interactions that take place between a T cell and antigen-presenting cell involve CD28/B7 and CD40L/CD40 pathways.^{104,105} There has been considerable interest recently in trying to block these pathways. Anergy is not automatically maintained once it is induced, and the continual presence of antigen has been shown to be required to maintain tolerance.^{106,107} Tolerance relying on anergy may also be a precarious state. It can be broken by infection and inflammation.^{108,109}

The blockade of these second signals uses antibodies (CD40, CTLA4) to specific receptors (CD40R, B27) to induce a peripheral form of tolerance. The concept that the presentation of antigen in certain situations could down-regulate the immune system is not new. Before the discovery of these receptors, previous investigators had noted that donor-specific blood transfusions appeared to increase graft survival, theoretically by presenting MHC antigens in a limited fashion and inducing a state of T-cell anergy rather than activation.¹¹⁰ The interruption of the CD40 and CD28 pathways (costimulatory blockade) at the time of transplantation has been demonstrated to induce a state of tolerance in several rodent models without any significant infectious or malignant complications. However, the application to the primate model has not replicated these results and has demonstrated only prolongation of allograft survival rather than tolerance. Several modifications of this technique are under study and may lead to a longer-lasting state of donor-specific T-cell anergy. Other methods of peripheral tolerance induction include donor antigen-presenting cell depletion or modification and anti-CD4 antibody to block T_H-cell function.¹¹¹ These peripheral methods of tolerance induction have not been as effective as the central mechanisms.

Immune regulation by regulatory cells

A role for active suppression in inducing and maintaining tolerance had been suggested by a number of studies. However, previously there had been an inability to propagate these cells *in vitro* or to identify these cells *in vivo*. This made it difficult to identify the mechanism involved. Thus, the mechanism of suppression remained controversial, despite a number of transplantation models that provided functional evidence for the existence of such cells.^{112–114} Significant progress has been achieved in the characterization of these suppressor/regulatory cells with the identification of a T-cell population that coexpresses CD4 and CD25 surface antigens.¹¹⁵

These CD4+ CD25+ T cells occur naturally in the thymus and represent a functionally distinct subpopulation of T cells. These cells have been characterized as a suppressive T-cell population that promotes tolerance to self and foreign antigens.¹¹⁶ In 2003, three independent groups showed that Forkhead box protein 3 (Foxp3), a nuclear transcription factor defective in the multisystemic autoimmune disease IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome),¹¹⁷ was expressed in CD4+ CD25+ T regs.^{19–21} Foxp3 was shown to correlate with suppressive activity and appears to regulate the expression of several cell surface molecules previously used to identify T regs, such as CTLA-4, GITR, and CD25 itself.²⁰

T regs can also be defined by their origin and are currently divided into two physiologically distinct groups. There are

the so-called natural (n) T regs that are thought to be generated intrathymically upon presentation of self antigen by thymic epithelial cells. The other category is the adaptive or induced (i) T regs that appear to be produced in the periphery, after an encounter with either self or foreign antigens. Several groups have confirmed that mature animal and human T cells can be converted from CD25– to CD25+ or Foxp3– to Foxp3+ in different experimental settings.^{30–34} Although both types of T regs share similarities, nT regs seem to have more stable expression of Foxp3.³⁵

An additional finding has been that individual populations of T regs may not only have different origins, but exhibit significant plasticity in the expression of their phenotype (much like T_H cells) depending on the cytokine milieu. Recent rodent data have shown that, after *ex vivo* manipulation of CD4+ CD25+ T regs with either Th1 or Th2 cytokines, the function of the cells can be quite different.³⁶ In certain circumstances these T regs (CD25+Foxp3+) can not only trigger the expansion of Th17-producing T cells but can also differentiate themselves into Th17 T cells *in vitro* upon stimulation with allogeneic antigen-presenting cells.^{37,38,118}

Several articles have reported a high proportion of circulating and intra-graft T regs in tolerant/stable patients in renal as well as liver and lung transplantation. In contrast, recipients with chronic rejection had significantly fewer T regs and lower levels of Foxp3 transcripts than clinically tolerant patients and healthy individuals. Mechanistic studies in renal transplant recipients confirmed that donor hyporesponsiveness was abrogated by depletion of CD4+ CD25+ high T cells. Thus, a technique to produce T regs could increase the durability of tolerance and perhaps be employed along with other tolerance induction techniques.

Transplantation in plastic surgery

Skin

Skin autograft

Autologous skin grafts can be of either full or partial thickness. The full-thickness skin graft gives an excellent cosmetic result with limited graft contraction but has the disadvantage of unreliable graft “take”. The amount of full-thickness skin graft is also limited by donor site availability. In cases in which large areas are to be covered, split-thickness skin grafting is used and is the most commonly practiced form of tissue transplantation in plastic surgery. It has the advantage of large available donor areas and better graft take but the disadvantage of increased graft contraction. Expansion of the split-thickness skin graft by meshing with expansion ratios from 1:1.5 to 1:9 is both useful and often essential in large burns.

Donor sites for split-thickness skin graft harvest may be limited in patients with extensive burns. This lack of available tissue has spurred the development of alternatives to conventional skin graft. Keratinocytes can be grown in culture with the ability to expand the available tissue 10000-fold.¹¹⁹ This technique has been applied in the treatment of large thermal injuries as well as leg ulcers and other benign conditions.¹²⁰ The reported disadvantages with cultured keratinocytes are

that they are more sensitive to bacterial contamination than are split-thickness grafts, and take has been reported to be poorer in comparison to meshed graft.¹²¹ They also blister spontaneously, are more susceptible to minor trauma, and contract more than do split-thickness skin grafts.¹²² These effects are related to a poorly developed dermis–epidermis junction.¹²³ The lack of a dermal component in these autologous grafts was overcome by a combination of cultured autologous keratinocytes and allogeneic dermis.¹²⁴ The technique has had favorable reports in patients with large burns, but the problem of an allogeneic dermis remains. Development of an acellular or “artificial” skin (Integra) consisting of dermal components, collagen, and a glycosaminoglycan overlaid with a sheet of Silastic addressed this antigenic problem.¹²⁵ A disadvantage of this approach is the need to skin graft the “dermis” after removal of the outer Silastic dressing. This has been superseded by seeding the graft with keratinocytes at the time of initial application.¹²⁶

A skin substitute containing allogeneic or xenogeneic structural proteins and ground substance seeded with autologous cells has also been described; it is composed of cultured autologous fibroblasts populating the dermis and cultured autologous keratinocytes covering the dermis.¹²⁷ These collagen gel dressings share the disadvantage of autologous cell culture in that cells require time in culture for expansion to usable numbers. An acellular dermal allograft available commercially is AlloDerm (LifeCell, Branchburg, NJ). A tissue-engineered living allogeneic dermal construct, Derma-graft (Advanced Tissue Sciences, La Jolla, CA) consists of human neonatal dermal fibroblasts seeded on to a synthetic mesh.¹²⁸ It has compared favorably with skin allograft as a temporary cover for severe burn wounds.¹²⁹ Another substitute is Graftskin (Organogenesis, Canton, MA), which is composed of a type I bovine collagen matrix seeded with allogeneic human fibroblasts and overlaid with allogeneic human keratinocytes.¹³⁰

Skin allograft

Skin allografts have been found to be beneficial in large burns either in combination with autograft or in isolation.^{131–135} Techniques such as use of widely meshed autologous split-thickness skin grafts with a meshed allograft overlay have been shown to have improved healing in comparison to autologous mesh alone. The availability of skin allografts has increased with the formation of regional tissue banks. Allogeneic skin may be frozen and banked in a manner that allows it to remain viable for a protracted period. Preservation with glycerol reduces the antigenicity of skin allografts and prolongs their survival.¹³⁶ Glycerol-treated grafts have been used in burn centers as coverage for burn wounds before autografting¹³⁷ or as composite grafts overlying widely meshed autografts.¹³³ However, the use of these grafts has been reported to lead to the production of antibodies that may inhibit the possibility of future VCA.

Factors that limit widespread use are that harvesting and banking services are not uniformly available, demand outstrips supply, and there is a small but significant risk of disease transmission. Cytomegalovirus infection, hepatitis, and human immunodeficiency virus infection have been reported in burn patients after cadaveric skin use.¹³⁸ Cultured allogeneic keratinocytes have also been used as a temporary

covering and will survive with immunosuppressive drugs.¹³⁹ Growth in culture is possible pre-emptively in burn treatment, but skin allografts are susceptible to rejection in addition to the problems associated with cultured autografts.

Skin xenograft

Porcine xenograft has been used as a temporary dressing in large burns with seeding of autologous grafts beneath it.¹⁴⁰ The application of xenogeneic dermis has also been found valuable in preparing a wound for subsequent grafting by stimulation of granulation tissue formation. The acellular artificial skin described by Burke *et al.*¹²⁵ uses a bovine collagen dermis that recipient fibroblasts repopulate. Xenogeneic tissue has limited uses in skin grafting because its cellular components are susceptible to hyperacute rejection.

Bone

Bone autograft

A series of basic histologic events follows transplantation of a bone autograft.¹⁴¹ After transplantation, the graft is surrounded by hematoma; the inflammatory cascade follows in which infiltration of inflammatory cells is followed by ingrowth of new vessels with removal and replacement of any dead or necrotic tissue. Nonvascularized grafts undergo necrosis, most of the osteocytes in the graft die, and only those on the surface that re-establish blood supply survive. The remainder of the graft is infiltrated by blood vessels from the recipient site and is repopulated by recipient osteocyte mesenchymal stem cells. Vascular ingrowth in cortical bone occurs through pre-existing haversian canals. There is an initial increase in osteoclast resorption activity, which increases the porosity and decreases the strength of the graft. Cancellous grafts are more rapidly revascularized by virtue of their open structure within 2–3 days. By comparison, revascularization of cortical grafts may take up to 2 months. The process in which vascular tissue invades the graft, bringing with it osteoblasts that deposit new bone, has been termed creeping substitution. Cortical bone shows incomplete resorption of necrotic bone, and the final graft mixture of living and dead bone does not approach the strength of a cancellous graft.¹⁴¹ Vascularized bone graft obviates the reparative phase of a nonvascularized graft and does not require a well-vascularized recipient bed. Biomechanically, vascularized bone grafts are superior to nonvascularized grafts.¹⁴²

Reconstruction of larger bone defects is limited by available autologous donor sites. An alternative being investigated experimentally is that of autologous osteocytes expanded in culture and grown in the recipient on polymer scaffolds.^{31,143}

Bone allograft

The advent of well-organized tissue banks and improved methods of bone graft sterilization and preservation have allowed the clinical use of large bone allografts.^{144–147} The use of frozen bone allograft has become a common practice for the reconstruction of long-bone defects, with an estimated annual volume of more than 200 000 procedures in the US.¹⁴⁸ MacKewen is credited with the first clinical use of allograft bone in 1881, followed by Lexer, Parrish, and others.^{141,149–152} Few if any of the donor cells in the nonvascularized bone graft

survive. The remaining bone acts as scaffold for ingrowth of recipient mesenchymal stem cells (osteocyte precursors) that repopulate the donor scaffold by creeping substitution. The larger graft acts as a mechanical spacer; because of slow union, long-term fixation is required, and as a result, the graft is susceptible to stress fracture and loosening of metal fixation devices. Large joint replacement has been in clinical practice for some time with mixed results. Parrish reported 50% collapse with use of frozen whole bone ends in 21 cases.¹⁵¹ Mixed results with use of large or smaller shell grafts for joint resurfacing or replacement after surgical excision have been reported.¹⁵³⁻¹⁵⁵ In craniofacial surgery, freeze-dried bone allografts have been used in midface advancements.¹⁵⁶ The infection rate was high, at 22%, but osteotomies healed in all patients. Bone allograft with autogenous bone chips has been reported in mandibular reconstruction.^{157,158} In hand surgery, bone allograft has been used to reconstruct defects after benign tumor removal and for traumatic or congenital defects.^{159,160} No major complications were reported, such as infections, fractures, or nonunion.

Vascularized allogeneic bone is susceptible to immunologic rejection.¹⁶¹⁻¹⁶⁴ The humoral and cellular response generated has a time sequence similar to that generated by any other allogeneic tissue.¹² Although individual bone cells express antigens, the predominant immunogenic cell in a bone allograft is thought to be bone marrow-derived.¹⁵⁰ Removal of marrow as in irradiation or by replacement with recipient marrow has been shown experimentally to prolong allograft survival.^{165,166} There has been a limited series of vascularized clinical allogeneic bone transplants (knee transplants) performed first under single-agent (cyclosporine) immunosuppression and later employing triple-drug immunosuppression.^{167,168} All of these grafts were lost within the first 56 months, regardless of the immunosuppression chosen. One confounding factor may be the addition of a vascularized skin paddle for immune monitoring that may actually increase the immunogenicity of the transplant.

Cartilage

Autologous cartilage

Cartilage is composed of chondrocytes within lacunae dispersed throughout a water-laden matrix. There are histologically three types: hyaline cartilage, elastic cartilage, and fibrocartilage. The matrix is composed predominantly of proteoglycans and type II collagen. Cartilage has no blood supply and relies on diffusion of nutrients and oxygen through the matrix. Chondrocytes, in contrast to osteocytes, have little reparative ability and heal by forming fibrous scar tissue.¹⁶⁹ The viscoelastic properties of the matrix provide cartilage with a “memory” in that it returns to its original shape after deformation; the variable water content in matrix causes a balanced tension within it and thus maintains its three-dimensional shape.

Cartilage autograft is used regularly for nasal, auricular, craniofacial, and joint surface reconstruction.¹⁷⁰⁻¹⁷² There are limited potential donor sites. Development of experimental tissue-engineering techniques has allowed the expansion of chondrocytes in culture to increase their numbers. These cells are seeded on to biodegradable polymers to form new autologous cartilage.^{31,143,173,174} Injectable polymer systems allow

delivery of autologous cartilage by needle, transcutaneously, or arthroscopically.¹⁷⁵⁻¹⁷⁷

Cartilage allograft

Chondrocytes express HLA antigens on their surface and are immunogenic.¹⁵³ The matrix is only weakly antigenic.¹⁷⁸ Surgical scoring or dicing with resultant exposure of allogeneic cells has been shown to hasten reabsorption of allogeneic cartilage.¹⁷⁹ Cartilage allografts have been used for applications similar to those of autologous cartilage.¹⁸⁰ Allogeneic cartilage can be either preserved or fresh. Preserved cartilage has the advantage of a more abundant supply without the risk of infection that is associated with the use of fresh cartilage.¹⁸¹⁻¹⁸³ Cartilage allograft, usually with irradiation pretreatment, has been used for volume augmentation in the facial skeleton. Despite initial good results in a large number of patients,¹⁸³ long-term data suggest a high rate of resorption.¹⁸⁴ Whether this is immunologically based or because preserved grafts tend to contain no viable cells is a matter for debate.¹⁸⁵ It has also been noted that smaller grafts are less susceptible than larger ones to graft volume loss.

Cartilage xenograft

Bovine-derived cartilage xenografts are susceptible to xenogeneic mechanisms of rejection, which results in a generally poorer outcome in comparison to either allogeneic or autogenous cartilage grafts. Attempts to modify these xenogeneic responses by altering the graft's immunologic stereotactic structure have been reported as being beneficial.¹⁸⁶

Nerve

Nerve autograft

The best clinical outcome after nerve transection is achieved with primary repair. Extensive injuries with a nerve gap require a nerve graft to achieve nerve repair without tension. The nerve graft undergoes the same degenerative process as in the distal recipient nerve after division.¹⁸⁷ What remains of the nerve graft is a myelin sheath with Schwann cells that act as a biologic conduit for the regenerating axons. The most common type of nerve graft is the interfascicular nerve graft, which joins fascicular groups to their distal matching group with an interposition nerve graft.¹⁸⁸ Other types in modern practice are fascicular nerve grafts (limited by matching proximal to distal fascicle) and vascularized nerve grafts, thought theoretically to be of advantage, although not of proven benefit clinically.¹⁸⁹ Other “conduits” have been used as nerve grafts,¹⁹⁰ such as silicone tubes seeded with Schwann cells, autologous vein, freeze-fractured autologous muscle, and pH tubes.¹⁹¹ Artificial conduits have demonstrated improved outcome when they have been seeded with autologous Schwann cells. None of the conduits to date has been found to be superior to nerve autograft.

Nerve allograft

Nerve autograft has a limited number of donor sites. In large nerve defects, nerve allograft has been used in a small number of patients. Immunologic rejection of nerve allograft can be prevented experimentally with immunosuppressive

drugs,^{192,193} and immunosuppressed axons will traverse the allogeneic graft in rodents^{194,195} and nonhuman primates.¹⁹⁶ Immunosuppression needs to be administered only while the recipient axons traverse the allograft and can then be terminated.^{197–199} Mackinnon *et al.* reported a series of 7 patients who underwent nerve allografting in the upper and lower extremities.^{190,200} Immunosuppression was stopped 6 months after nerve regeneration across the allografts. All but one patient demonstrated return of motor and sensory functions.

Limb and composite tissues

Microvascular autogenous tissue transfer is a well-established reconstructive modality. Available donor sites limit the autologous transplants of tissue. In addition these donor sites can be associated with potential morbidity. The ability to use allogeneic limb or vascularized composite tissues such as skin, subcutaneous tissues, muscle, bone, blood vessel, and nerve has greatly expanded the realm of reconstructive surgery. Extensive skeletal and soft-tissue defects or even whole limbs have been replaced. However, nonautogenous tissue is susceptible to immunologically mediated rejection with subsequent graft loss, and prolonged immunosuppression is the only way at present to attain long-term allograft survival. To make composite tissue transplantation clinically feasible, consideration should be given to its technical, functional, and immunologic aspects.

Technical considerations

Transplantation of vascularized limb or composite tissues was made possible by the microsurgical techniques first developed by Carrel and Guthrie in 1906.^{201,202} Microvascular anastomoses and revascularization have become routine practice in large centers, with success rates in excess of 90%.^{203,204} In contrast to acute traumatic cases, such as replantation, allogeneic transplantation has been performed in elective settings after appropriate preparation, such as preoperative angiography and donor selection. The operative techniques are based on the current advances in bone, tendon, and nerve repairs.

Functional considerations

Normal wound healing and bone growth occur in transplanted composite tissue allografts after experimental transplantation in various animal models.^{26,205} Return of neuromuscular function has been observed in limb allografts of animals treated with immunosuppression,^{206,207} including those in the primates,^{208–210} while in clinical hand transplants both motor and sensory recovery have been reported.^{5,211,212} Thus, functional recovery after allogeneic transplantation appears to follow the same principles as in nontransplant situations and is influenced by the recipient's age, systemic factors, and associated local injuries.

Immunologic considerations

A limb or vascularized composite allograft consists of multiple discrete tissue components, such as skin, subcutaneous tissue, muscle, and bone, and each tissue has been shown to be strongly antigenic.¹⁰⁶ Both animal data and the current clinical human experience have confirmed the need for significant

host immunosuppression to prevent allograft rejection. The potential adverse effects of indefinite, multiple-agent immunosuppression are difficult to justify in the opinions of many for a surgical procedure aimed at improving quality of life.^{14,213} This debate over the risk–benefit balance has continued since the first successful human hand transplantation. However, both the proponents and critics of the current transplants agree that significant reduction of host immunosuppression, and particularly tolerance induction to the allografts, would help achieve widespread clinical application of composite tissue allografts.

Experimental limb transplantation

Limb allograft transplantation is possible experimentally with different immunosuppressive regimens.^{205–207,209,214–222} Immune modulation techniques that decrease the antigenicity of specific components of a limb allograft were shown to prolong survival.¹⁶⁶ Although sporadic incidents of tolerance have been reported after cessation of immunosuppressants,^{216,223} long-term immunosuppression was generally necessary to prevent allograft rejection. Combination therapy with cyclosporine and MMF was more effective than monotherapy.²²⁴ Although rat models provide important information on limb allograft transplantation, the rodent immune system is fundamentally different from that of the human. A large animal model such as a canine, pig, or primate offers a much closer analogy to the human immune system.

Ustuner *et al.* reported transplantation of a radial forelimb osteomyocutaneous flap between size-matched outbred swine with use of a daily cyclosporine, MMF, and prednisone oral regimen.²²³ Of the eight swine, two sustained severe rejection, three demonstrated mild to moderate rejection, and three were free of rejection at the termination of the experiment at 90 days. No drug toxicity was evident in serum hematologic and chemical parameters of immunosuppressed animals. The Louisville group also examined the use of FK506, MMF, and prednisone in the same swine model.²²⁵ Five of nine animals that survived to the study end at 90 days were noted to be free of rejection. However, this combination of immunosuppressants resulted in significant mortality and morbidity, including abscesses, diarrhea, weight loss, and pneumonia.

Lee *et al.* sought to achieve host tolerance to musculoskeletal allografts through matching of the MHC antigens between donor and host swine with only a 12-day course of cyclosporine.²²⁶ Allografts from MHC-mismatched donors treated with cyclosporine and allografts from MHC-matched (minor antigen-mismatched) donors not treated with cyclosporine were rejected. However, allografts from MHC-matched donors treated with 12 days of cyclosporine showed no evidence of rejection until sacrifice up to 47 weeks after transplantation. Thus, genetic matching may alleviate the need for immunosuppression after limb transplantation. MHC matching can be extended beyond family members, for example, as the National Bone Marrow Registry exists to match MHC of unrelated individuals.

More recently, Kuo *et al.* demonstrated that the use of mesenchymal stem cells combined with bone marrow transplantation, irradiation, and short-term immunosuppressant therapy could prolong CTA survival (>200 days) in a swine hind-limb model.²²⁷ The authors suggested that the regulatory

activity of the mesenchymal stem cells might be contributing to the prolongation seen in this model.

The primate model offers the closest imitation to human limb transplantation in anatomy and immune system. In the 1980s, four studies of limb allograft transplantation were performed on nonhuman primates.^{209,210,222,228} All of the studies involved the transplantation of a hand and use of high-dose cyclosporine and steroids. Many of the animals suffered multiple infectious complications, with some succumbing to fatal malignant neoplasms resulting from high levels of immunosuppression. Nonetheless, few primates demonstrated prolonged survival of their allografts. These studies confirmed the existing rodent and canine data that cyclosporine monotherapy is ineffective in preventing limb allograft rejection, even at toxic doses. Few allografts survived long enough for functional recovery to be ascertained. More recently, Barth *et al.* performed heterotopic transplants of composite facial subunits consisting of skin, muscle, and bone in mismatched *Cynomolgus* macaques.²²⁹ They attempted to use high-dose tacrolimus monotherapy via continuous intravenous infusion for 28 days, which was then tapered to daily intramuscular doses. They had initially hoped that this limited course of high-dose tacrolimus would lead to tolerance, as had been observed in the swine kidney model. Although this protocol of tacrolimus monotherapy did provide prolonged rejection-free survival of the allografts, it was associated with the development of a high frequency of donor-derived post-transplant lymphoproliferative disorder tumors. No study has been performed in primates with combination immunosuppressant therapy. The application of such a regimen could provide insight into nerve regeneration, bone healing, and ultimate recovery of function. Cendales's group examined the possibility of using belatacept in combination with tacrolimus in a primate model of hand transplantation. Compared to tacrolimus, the addition of belatacept improved rejection-free allograft survival.²³⁰ They also found that when they combined belatacept with rapamycin there was unacceptably high rates of wound failure in skin-containing transplants.

Hand transplantation

Currently, clinical hand transplantation remains an experimental procedure, and the long-term outcomes of this innovative procedure are still being determined. In the current era of immunosuppression, there are 107 known transplanted hand/upper extremities in 72 patients (Table 32.3).^{5,11,211,212,231–235} The results thus far have demonstrated that hand transplantation is technically feasible and the outcomes are promising, with patients reporting varying degrees of return of function. The support for the application of hand transplantation from hand surgeons has been strongest for those patients who have lost both hands.¹⁴ While most programs continue to perform transplants under their local institutional review board guidelines, several programs have proposed bilateral hand transplantation as the standard of care for bilateral amputation but no center has performed a transplant without an IRB protocol. The support for unilateral transplantation has been much lower from the surgical community. However, patients who have undergone unilateral hand transplants have reported the restoration of self as well as return of function. Thus, while function is a critical outcome for the

measurement of success, the restoration of the patient's well-being and sense of self must also be considered in the evaluation of hand transplantation.

The major issues in hand transplantation are the need for maintenance immunosuppression and the evaluation of the functional outcomes of the transplants.^{236,237} There are well-known risks to the transplant recipient related to the use of chronic immunosuppression. These include complications such as an increased susceptibility to opportunistic infections, renal dysfunction related to the use of calcineurin inhibitor-based medications (tacrolimus and cyclosporine), and an increased incidence of malignancies. In addition, despite the use of modern immunosuppression regimens, the majority of the transplants experience episodes of acute rejection and will likely face chronic rejection. The functional outcomes have been, for the most part, favorable but the current challenge remains to improve nerve recovery and the restoration of function of the intrinsic muscles of the hand.

Immunosuppression and transplant survival

The emergence of hand transplantations and the field of reconstructive transplantation have not corresponded to any recent breakthrough in transplantation immunology. It is clear from the 1-year survival data of such highly antigenic transplants as the lung and intestine that the current potent immunosuppressant drugs can prevent the fulminant rejection of even highly antigenic tissues, as long as sufficiently high doses of different agents are used.^{238,239} This has been replicated in the hand transplantation literature as there has been an excellent 1-year survival of the transplants.⁵ Thus, the critical issue continues to be how much immunosuppression, and lifelong morbidity, can be justified for a nonlife-saving procedure.

There is significant variability in medications employed to maintain the hand transplants, making it difficult to conclude the superiority of one immunosuppressive regimen over another. This type of conclusive evidence will only be derived from prospective, randomized clinical trials. Therefore, as this technique expands, it will be important to organize multicenter trials to determine the best practice for the use of immunosuppression after hand transplantation.

Currently, the majority of the transplant programs have employed the use of an induction agent such as IL-2 receptor blocker (basiliximab), ATG, or the anti-CD52 monoclonal antibody (alemtuzumab). There was an initial trend towards using more anti-CD52 monoclonal antibody in hand transplant patients but the use of this drug has decreased more recently.²⁴⁰ The Louisville group initially used the IL-2 receptor blocker (basiliximab) on its first 2 patients as the sole induction agent but then switched to alemtuzumab on all subsequent patients,²¹¹ while the Lyons group relied solely on ATG on all its patients.²¹² More recently, groups at the Johns Hopkins University and the University of Pittsburgh have implemented a program to move beyond the current three-drug regimen. They have employed alemtuzumab induction therapy as an integral part of their "Pittsburgh/Johns Hopkins University protocol" that uses donor bone marrow infusion in combination with tacrolimus monotherapy in an attempt to reduce the amount of chronic immunosuppression needed and thereby improve the risk-benefit balance.

Table 32.3 Upper extremity transplant performed worldwide

Center (country)	Unilateral Tx	Bilateral Tx	Total limbs Tx	Total limb Tx lost	Mortalities
Melbourne (Australia)	1		1		
Innsbruck (Austria)	1	4	9		
Brussels (Belgium)	1		1		
Six centers (China)	9	3	15	7	
Lyon (France)	1	5	11	1	
Paris (France)		1	2	2	1
Munich (Germany)		1	2		
Tehran (Iran)	1		1		
Milan (Italy)	3		3		
Monza (Italy)		1	2		
Selayang (Malaysia)	1		1		
Mexico City (Mexico)		2	4	2	1
Wroclaw (Poland)	5	1	7	1	
Madrid (Spain)		1	2		
Valencia (Spain)		3	6		
Ankara (Turkey)		1	2	2	1
Antalya (Turkey)		3	6	2	1
Leeds (United Kingdom)	1		1		
Brigham and Women's Hospital (USA)		2	4	2	
Emory (USA)	1	1	3	2	
University of Pittsburgh/Johns Hopkins (USA)	2	4	10	2	
Massachusetts General Hospital (USA)	1		1		
University of Louisville (USA)	7	1	9	1	
UCLA (USA)	1		1	1	
University of Pennsylvania (USA)		1	2		
Wilford Hall, Medical Center (USA)	1		1		
Totals	37	35	107	25	4

The most common maintenance immunosuppressive regimen used in hand transplantation has been a continuous administration of low-dose steroid with tacrolimus, and MMF. However, over time several teams have changed from tacrolimus to sirolimus treatment to avoid the side effects, such as hyperglycemia or renal insufficiency.⁵ In some cases, the teams attempted to decrease the immunosuppressive medications and wean or eliminate steroids from the regimes. However, while such strategies have been successful in the renal transplant literature, in these hand transplants evidence of myointimal hyperplasia has been noted. In addition, one of the hand transplants in Louisville was lost due to what appeared to be chronic rejection after being maintained on reduced immunosuppression protocol.^{231,241} Thus, it may not be possible simply to transfer protocols that have demonstrated results in renal transplantation directly to hand transplantation.

Measuring outcomes in hand transplantation

The accurate evaluation of the functional outcome of the hand transplant patient is critical to determining the value of this

nonlife-saving transplant. Currently, there is some variation in the tools that are employed to quantify the function of the hand transplant. While the Louisville group has reported much of the functional outcomes in publications based on the Carroll test (a well-validated test that evaluates the patient's ability to perform activities of daily life that involve the upper limb),²⁴² the International Registry on Hand and Composite Tissue Transplantation bases its functional outcomes on its own Hand Transplantation Score System (HTSS).^{5,211} This evaluates six aspects of the hand transplant: (1) appearance (15 points); (2) sensibility (20 points); (3) motility (20 points); (4) psychological and social acceptance (15 points); (5) daily activities and work status (15 points); and (6) patient satisfaction (15 points). A total result of 81–100 points is graded as an excellent outcome, 61–80 as good, 31–60 as fair, and 0–30 as poor. The University of Pittsburgh bases its evaluation of patients on measurement of active range of motion, passive range of motion, grip strength, pinch strength, and two-point discrimination. They also use the Semmes–Weinstein evaluation to document the sensory return of the transplants. Early results from this group show that all their patients

demonstrate sustained improvements in motor function and sensory return correlating with the time after transplantation and level of amputation.

All of the hand transplantation programs have used the Disabilities of the Arm, Shoulder and Hand (DASH) score to evaluate patients post-transplant.²⁴³ The DASH Outcome Measure is a 30-item self-report questionnaire designed to measure physical function and symptoms in people with any of several musculoskeletal disorders of the upper limb. The tool is a single reliable instrument that can be used to assess any or all joints in the upper extremity.

The longest follow-up available is from the second hand transplant performed by the group in Louisville; the patient is now more than 18 years postoperative with a functioning hand. In a recent article, the group in Louisville reported detailed outcomes of the first two American hand transplant recipients at 8 and 6 years post-transplantation.^{211,231} Both patients have allograft survival, with improvements in intrinsic muscle activity, total active motion, and return of functional grip, pinch strength, and sensibility. The latest Carroll test scores, which measure patients' ability to perform tasks requiring a combination of mobility, motor function, and sensation, are fair for patient 1 (72/99) and fair for patient 2 (55/99). These Carroll test scores exceed the expected results of 20–30 of 99 that would be achieved with a prosthetic hand. The first patient's Semmes–Weinstein monofilament sensation testing is in the normal range for all fingertips, and the patient has shown improvement in both static two-point discrimination and moving two-point discrimination over previous testing. Touch localization, stereognosis, and temperature and vibration sensation have also returned. The second patient has not demonstrated a similar return of sensation through year 6; however, in 2008, his protective sensation was noted to have returned. In a more recent update they reported the results of their third patient in which they stated the Carroll score was 57 at the yearly checkup. The range of motion with active digital motion was approximately 45% of normal. Sensory evaluation showed advancement of Tinel's sign to fingertips, diminished protective function, and light touch localization in the index, ring, and small fingers only.

The International Registry reported that, based on the HTSS scale, the majority of patients demonstrated good results from the hand transplant procedure.⁵ They noted that from a functional point of view there was good recovery in the majority of the transplanted hands. However, the recovery of motor function was limited to the larger muscle groups but they often enabled the patients to perform most daily activities. The level of satisfaction was slightly higher in the bilateral hand-transplanted patients when compared to unilateral patients. All of the patients developed protective sensation (31 patients analyzed with a minimum of 1-year follow-up) and 90% regained tactile sensibility. The time to development of distal sensory and motor recovery was correlated to the level of amputation. It was noted that the more distal the level of amputation, the faster the recovery of the transplanted hand. This finding has called into question the level at which to offer a hand transplant but currently there are no firm recommendations from any of the active groups.

Several of the groups included in the international registry analysis have also published individual reports. The group from Poland has recently published follow-up on two patients who have undergone successful hand transplantation.²³³ The

first patient was 3 years out at the time of publication and has demonstrated total active motion of fingers equal to 63% of that of his unaffected hand. His DASH score was reported as 95 and the patient returned to work 20 months after the transplant. The second patient was only 6 months post-transplant and scored 85 points on the DASH questionnaire. The surgeons reported that the Semmes–Weinstein monofilament test had documented 15 mm two-point discrimination and the transplanted hand grip strength reached 4 kg. This patient had also returned to a full-time job.

The Lyon group documented the late results of their two bilateral hand transplant patients.^{212,244} Both patients have recovered pain and cold sensations, without dysesthesia or cold intolerance. The first recipient, 6 years after transplantation when the paper was published, had a Semmes–Weinstein test that demonstrated sensitivity recovery on the right hand using 2.83–3.61 monofilaments and on the left hand using monofilaments between 3.22 and 4.08. The average two-point discrimination test was 6 mm on the right hand and 9 mm on the left hand. In contrast, the second patient's Semmes–Weinstein test demonstrated sensitivity recovery on the right side using 3.22–3.61 monofilaments and on the left side using monofilaments between 3.22 and 3.84. However, muscle strength was diminished in both patients. The first patient had bimanual grip strength of 12 kg and the second patient's grip strength was 4 kg on the right side and 8 kg on the left side.

While the authors from Lyon comment that manual dexterity evaluated using the Minnesota and Carroll test demonstrated a normal capacity for reaching, grasping, moving, positioning, and turning the objects, they did not provide scores for these tests. They did comment that the first recipient continued to have impairment to lateral pinch and bimanual grasp. The patients were, according to the authors, able to perform the majority of daily activities by the first year after transplantation. One of the two patients had returned to work.

Finally, the Innsbruck group has published an 8-year follow-up after hand transplantation.²⁴⁵ One of the most significant findings from this group is that patients can continue to observe improvement of their function and sensation even at years 4 and 5 after transplant. Their first patient demonstrated excellent recovery after bilateral hand transplantation. Eight years after transplantation, hand function in this patient was outstanding. He is able to use his hands symmetrically, performing all activities of daily life. The current DASH score is 34. The second patient was a forearm transplant who has experienced continuous improvement of motor function during the first 3 years and, according to the authors, has satisfactory hand function. The patient noted that the hand function is superior to that he had achieved with myoelectric prostheses. While the patient has noted recovery of hot and cold discrimination (at 6 months after transplantation), his overall sensitivity remains poor with no detectable two-point discrimination. Grip strength measured 6.8 kg on the right side and 5.5 kg on the left side. However, compared with results after hand transplantation, fine motor skills were slightly inferior in our forearm transplant patient. The third patient was still in the process of undergoing intensive outpatient therapy at the time of the publication.

The world experience in hand transplantation demonstrates the clinical utility of this emerging technique. However, there are many questions that are currently unanswered. These

questions surround the best use of immunosuppression and immunosuppressive regimens. It highlights the importance for future collaborations between centers to address best practice in the immunosuppression regimen. This review also reveals the need for continued collaborations between groups to standardize the way in which functional outcomes are measured so that case outcomes can be compared more easily.

Facial transplantation

A total of 37 face transplants have been performed (20 partial and 17 full face) from 2005 to December 2015 (Table 32.4).¹⁰ There are some discrepancies between actual transplantations performed and those reported in peer-reviewed journals, with some underreporting of the transplants performed. All of the patients have experienced rejection episodes but the majority of these have been successfully treated. These transplants have restored form and function in the majority of the patients.

Post-transplant malignancies have increased in incidence, and a total of six patients have died. The first face transplant patient, performed in Lyon, France, recently died secondary to non-small cell lung cancer likely related to her history of smoking. She also exhibited donor specific antigen that may have led to the rejection of her sentinel flap and later her lower face. The second face transplant patient died secondary to non-compliance with his medications. The other deaths were related to recurrent head and neck cancer and necrotizing infection after attempted combined hand and face transplant.^{246–248}

Future of transplantation in plastic surgery

The current strategy for the post-transplant management of composite tissue allograft is to treat them with well-established regimens of immunosuppression used in solid-organ transplantation. The majority of VCA transplant patients have been treated with an induction agent (such as ATG or alemtuzumab) and then maintained with up to three immunosuppressive medications (tacrolimus, MMF, and steroids). This has led to a high level of success in terms of initial graft survival. It has not prevented episodes of acute or chronic rejection. However, in order for the field of reconstructive transplantation to expand its indications beyond the current limited experience, techniques need to be designed either to significantly reduce or eliminate the need for chronic immunosuppression. The future direction of this field is heavily dependent on the development of innovative approaches to the use of immunosuppressive agents and tolerance induction protocols.

Many still regard the use of chronic immunosuppression to achieve transplantation of limb or a facial allograft difficult to justify clinically.²⁴⁹ Development of effective regimens to induce host tolerance without long-term immunosuppression, therefore, is essential to alter the risk–benefit balance. Such regimens may involve site-specific immunosuppression directed at the graft, monoclonal antibodies that block a particular step in the process of antigen recognition, or exposure to donor antigen with the introduction of hematopoietic stem cells either before or at the time of transplantation to establish a state of mixed chimerism.²⁵⁰

T-cell-depleting therapies have been effective at promoting graft acceptance and tolerance in several animal models.^{251,252} However, clinical translation of these protocols had not yielded significant progress until the introduction of the anti-CD52 monoclonal antibody, alemtuzumab (Campath-1H). CD52 is expressed on most T and B lymphocytes, NK cells and monocytes, and alemtuzumab rapidly depletes these cells with varying kinetics of repopulation. The initial clinical reports by Calne *et al.*^{90,91} suggested that the use of alemtuzumab in combination with low-dose cyclosporine in kidney transplantation could achieve a state of “prope” tolerance (graft acceptance with reduced immunosuppression). However, the use of alemtuzumab alone or in combination with deoxyspergualin led to 100% acute rejection.^{253,254} This demonstrated that alemtuzumab was not in itself tolerogenic. Its use as an induction agent has recently been demonstrated to significantly reduce the episodes of biopsy-proven acute rejection (14% versus 26%) when compared with thymoglobulin. However, there was no difference in survival, initial length of stay, and maintenance immunosuppression (including early steroid elimination).²⁵⁵ Attempts to use T-cell depletion agents such as alemtuzumab or ATG in the field of CTA have yielded similar results and highlight the need for additional strategies to allow for the reduction of immunosuppression.

VCA offers some unique advantages to develop innovative treatment protocols, such as continuous monitoring and adequate biopsy sampling of the graft by simple visual inspection of the skin, allowing for a timely intervention, treatment, and precise adjustments of immunosuppression on an individualized basis. In addition, some VCAs may contain varying amounts of donor bone marrow and a vascularized bone marrow niche, which could serve as a continuous source of donor cells, including bone marrow-derived stem cells. This has been demonstrated in certain experimental animal models to modulate the host immune response favorably. Hence, novel cell-based strategies to minimize immunosuppression or induce immune tolerance are particularly appealing in VCA.

The group at Johns Hopkins University introduced a strategy (while at the University of Pittsburgh), that takes advantage of the cellular depletion provided by alemtuzumab, combining it with a delayed donor bone marrow cell infusion. This technique had some reported success with living related kidney transplants; and appears to enable minimization of the maintenance of immunosuppression after liver, pancreas, heart and lung transplantation. They performed 8 hand/forearm transplants in 5 patients under this protocol at the University of Pittsburgh. The recipients have been maintained on a single immunosuppressive drug (tacrolimus) at low levels and continue to have increased motor and sensory function of their transplanted hands. Despite the combination of alemtuzumab induction and the donor bone marrow cell infusion, all of the transplants have experienced at least one episode of acute rejection that required additional treatment. However, acute episodes of skin rejection observed with this protocol were responsive to topical therapy alone in about 50% of cases or short courses of steroids. Both superficial and deep tissue biopsies as well as high-resolution ultrasound did not show any evidence of vascular myointimal proliferation as an indirect sign of chronic rejection. This bone marrow cell-based immunomodulatory protocol has been proven to be well tolerated and efficacious and has allowed hand/

Table 32.4 Face transplants performed worldwide

Center (country)	Partial face patients	Total face patients	Total face transplants	Mortalities
Amiens (France)	3		3	1
Xi'an (China)	1		1	1
Paris (France)	6	1	7	2
Brigham and Women's Hospital (USA)	3	4	7	
Valencia (Spain)	1		1	1
Seville (Spain)	1		1	
Barcelona (Spain)		2	2	
Ghent (Belgium)		1	1	
Antalya (Turkey)	2	3	5	1
Ankara (Turkey)	1	1	2	
University of Maryland (USA)		1	1	
Gliwice (Poland)		2	2	
Cleveland Clinic (USA)	2		2	
St. Petersburg (Russia)		1	1	
New York University (USA)		1	1	
Total	20	17	37	6

forearm transplantation with low-dose tacrolimus monotherapy but does not appear to allow for the complete withdrawal of all immunosuppression. Unfortunately two of the patients had issues with compliance and have had their unilateral hand transplants removed. There are still three from the original group, and two more recent transplants have been performed at Johns Hopkins. Long-term data and follow-up, however, are still needed to confirm these findings.

The use of a single antibody may not have the ability to lead to tolerance of donor antigen. Thus the addition of other monoclonal antibodies, such as CD40 ligand, may be needed to produce a state of T-cell anergy to these antigens. It has been observed that full activation of T cells requires both cell–cell interaction and simultaneous delivery of costimulatory signals. A T cell that encounters foreign antigen in the absence of necessary cytokines fails to activate, which may lead to a state of tolerance.²⁵⁶ This mechanism is based on the blockade of CD28/CTLA4–CD80 and the CD40–CD40 ligand (CD154) pathways.^{257,258} Several nonhuman primate tolerance models to evaluate the effect of interrupting these critical pathways have demonstrated prolonged survival of renal allografts.^{259,260} It remains to be seen whether such strategies could allow limb transplantations to be performed with the ultimate cessation of immunosuppression.

However, it currently appears that T-cell depletion alone (with or without bone marrow) or the reliance on other antibodies is unlikely to lead to tolerance of organ allografts. Regimens that lead to the induction of mixed hematopoietic chimerism, however, have been shown to lead to tolerance of organ allografts in multiple preclinical studies.^{100,261–263} The strategy involves the use of bone marrow or stem cells to induce a state of mixed chimerism. Owen observed more than half a century ago that it is possible to induce tolerance by exposing the donor's bone marrow to the recipient's immune system before its maturity.²⁶⁴ Such fetal or neonatal induction

of tolerance for musculoskeletal allografts has been achieved in experimental swine and rodent models, respectively.^{265–267} Successful adaptation of this approach could even have therapeutic potential for congenital conditions. Similar application of mixed chimerism protocols could also lead to tolerance induction in adults.^{100,268} Foster *et al.* demonstrated that rodent mixed chimeras would accept syngeneic donor limb allografts.²⁶⁹ Huang *et al.* have used a minimally toxic protocol to generate mixed chimeras in the miniature swine with *in vitro* donor-specific tolerance while preserving immunocompetence to third-party antigens.^{270,271} Employing a similar strategy in the same model, Hettiaratchy *et al.* demonstrated tolerance to the muscle and bone portions of VCA allografts across a major MHC barrier.²⁷² In addition, case reports have shown tolerance to a kidney allograft in patients who received a bone marrow transplant from the same donor, sometimes years apart.^{273–275} However, the combination of most conditioning regimens combined with the infusion of bone marrow often results in GvHD. The greater the genetic disparity between the bone marrow recipient and the donor, the more likely the recipient will develop GvHD.

These findings led Sachs and colleagues to embark on a clinical trial using this approach to attempt to induce tolerance in patients with end-stage renal disease and advanced multiple myeloma using HLA-identical sibling donors.²⁷⁶ Six patients received cyclophosphamide, ATG, and thymic irradiation as well as cyclosporine (which was tapered off after 2 months) and subsequently followed by donor leukocyte infusions to improve graft-versus-tumor effects.^{277,278} All patients demonstrated initial engraftment of the donor marrow but the donor cell chimerism was lost in all of the patients except two. These two patients converted to full donor chimerism and had to be treated for GvHD. The other 4 patients maintained long-term renal function (up to >9 years) in the absence of immunosuppression. One of the 4 patients did have a single

rejection episode that was controlled by the transient use of immunosuppression.

The group recently modified its protocol to address the induction of tolerance in recipient kidneys from HLA-mismatched living donors. To reduce the risk of GvHD they now use an anti-CD2 monoclonal antibody (siplizumab or MEDI-507) for its T-cell depletion rather than ATG. Five patients received cyclophosphamide, MEDI-507, thymic irradiation, and cyclosporine.²⁷⁹ Occurrences of humoral rejection and engraftment syndrome led to the addition of rituximab and corticosteroids for the last 2 patients.²⁸⁰ Mixed chimerism was

transiently achieved in all patients but donor cells could not be detected after day 21 and GvHD did not develop. One patient lost his kidney graft as a result of an early and irreversible antibody-mediated rejection. In the other 4 patients, immunosuppression was successfully withdrawn during the first year post-transplant and normal renal function has been sustained for more than 3–6 years to date. The mechanisms underlying this operational tolerance are not fully elucidated. This model is also designed for living related transplants and in its current form would not be possible for VCA transplants.



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Technology innovation in plastic surgery: A practical guide for the surgeon innovator

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SYNOPSIS

- Plastic surgeons have historically been distinguished by their ability to innovate and should continue to maintain this competitive advantage.
- This chapter will familiarize the surgeon innovator with a systematic approach to innovation. This process includes idea formation, valuation, funding, intellectual property, institutional technology transfer, the FDA regulatory process, and conflicts of interest.
- Negative pressure wound therapy, acellular dermal matrix, and noninvasive body contouring are used to discuss the impact of innovation within plastic and reconstructive surgery.

Introduction

Innovation drives the advancement of medicine. Recent medical innovations, from evidence-based medicine and information technology to robotic and laparoscopic surgery, have revolutionized the practice of medicine. In the surgical arena, innovation has led to increasingly effective and less invasive therapies resulting in better patient care.

What separates invention from innovation? Invention is the formulation of new ideas for products or processes, while innovation creates the application of new inventions. In business, invention uses cash to create a product and innovation takes a product and creates cash. In medicine, invention is an attempt to create a solution to a clinical problem and innovation drives the solution to the bedside – analogous to the process by which translational research applies basic science to clinical problems.¹

Plastic surgeons, by trade, are innovators. We devise innovative solutions to difficult problems. Our competitive advantage lies in innovation. Unlike the neurosurgeon or cardiologist, we do not lay claim to any one part of the body.² In the hospital we are called upon for our creative solutions to the neurosurgeon's need for calvarial reconstruction, the cardiac surgeon's need for chest wall reconstruction, and the orthopedic surgeon's need for hardware coverage.

Our innovative spirit transcends beyond innovative surgical methods and encompasses innovation of novel technologies as well. Historically, microsurgery, distraction osteogenesis, tissue expansion, endoscopic plastic surgery, liposuction and laser technology have all served as platforms for expanding the scope of our practice, as well as expanding the scope of what we can offer our patients.³

The expansive breadth of plastic surgery exposes our field to multiple competing subspecialists. Dermatologists, otolaryngologists, ophthalmologists, obstetricians and internists are increasingly involved in aesthetic surgery. Similarly, general surgeons are competing for abdominal wall reconstruction, breast reconstruction, and wound healing. Otolaryngologists compete for head and neck reconstruction. Orthopedic surgeons compete for hand cases. Each of these fields involves important new innovations, and subsequently opportunities for patient care, research, and revenue. Aesthetic surgery is riddled with novel technologies including skin resurfacing techniques, noninvasive body contouring, injectables, and laser therapy. The attractive revenue stream in this cash-based field is obvious and draws in more and more competition. Similarly, abdominal wall reconstruction has been revolutionized by the introduction of new biomaterials. Breast reconstruction is changing with the introduction of new breast implants, fat grafting and dermal substitutes. The field of wound healing has dramatically changed with negative pressure wound therapy. Head and neck reconstruction has seen the introduction of bioabsorbable plates, screws and alloplastic bone substitutes, while PyroCarbon arthroplasty and artificial nerve conduits continue to expand the offerings of hand surgery. Innovation is the sustainable competitive advantage for plastic surgeons in this competitive clinical reality.

Today, however, the arena of medical innovation is far more complex than it was 50 years ago. There is more scrutiny from the US Food and Drug Administration, an exponential growth in the number of patents filed and more complexity in regulatory pathways for new medical products. In the setting of a healthcare and economic crisis, it is harder to

justify increased development expenses with increased competition for limited investment funds. When the surgeon is asked to innovate, he/she also faces a plethora of challenges unique to the surgeon innovator including conflict of interest concerns and navigating within the confines of the intellectual property claims of universities.⁴ The challenges faced by today's surgeon innovator are captured well by Machiavelli's *The Prince*: "There's nothing more difficult to plan, nor more dubious of success, nor more dangerous to manage than the creation of a new order of things. Whenever his enemies have the ability to attack the innovator, they will do so with a passion of partisans while others defend him sluggishly so that the innovator and his party are likely to be vulnerable." The enterprise of surgical innovation may receive little support and face many barriers, however it can create new technologies that may revolutionize a field and impact millions of patients. To overcome today's barriers to surgical innovation, we must create and use a systematic approach to translate ideas based on a human problem into a product that can change clinical practice.⁵ This chapter sets out to discuss a systematic approach to surgical innovation and gives a few examples of new technologies in our field.

The idea

Mark Twain said, "The name of the greatest of all inventors is accident." In 1957, Mason Sones accidentally injected the right coronary artery with dye, he immediately recognized the problem and pulled the catheter out while the injection of dye continued. He later said, "That day I realized that I had discovered something very important." He then went on to refine the technique that led to coronary angiography. On the other hand, Plato's frequently cited proverb, "necessity is the mother of invention" hints that innovation certainly does not need to rely on an accidental discovery.

Today, there are calculated and systematic innovation paradigms that start with the identification of a clinical problem. The problem should be an unmet clinical need. The scientific knowledge in the arena and the limitations of the current solutions should then be explored. The clinical problem can be taken to the laboratory or into multidisciplinary think boxes where a solution is systematically developed, with the hope of translating it back to the operating room. Robert Frost thought that ideas are feats of association, "Having what is in front of you brings up something in your mind that you almost didn't know you knew." This paradigm of discovery may describe why the majority of surgical devices are rooted in the ideas of observant surgeons. The timeless story of Dr. Thomas Fogarty's development of the Fogarty catheter started with a defined clinical problem and was assisted with "feats of association." Fogarty was a scrub technician and witnessed acute limb loss as a result of surgery to remove blood clots. As a medical student of the University of Cincinnati, he started to work on a solution to the clinical problem he had identified years previously. In his garage, he developed a balloon on the tip of a catheter that could be inserted through a small access incision and passed through the artery beyond the blockage. Once past the blockage, the balloon could be inflated and the clot dragged out of the artery. His ability to invent and prototype this novel device was perhaps facilitated by his prior association with surgical tools as a scrub

technician. He met much criticism from his mentors but went on to patent the balloon catheter, built the device in his garage, and worked tirelessly to have the catheter adopted by vascular surgeons. The Fogarty catheter has since revolutionized vascular surgery and led to a platform for innovations in minimally invasive techniques.

Whether accidental or systematically created, the idea behind an innovation can lead to the development of two broad categories of innovations: a novel method or a novel device. Because the majority of the chapter discusses medical devices, we will briefly discuss the innovation of novel methods. Delos Cosgrove describes his idea for a novel surgical method: "Several years ago, in preparation to perform aortic valve replacement, I found the ascending aorta entirely calcified and both femoral arteries occluded. Recognizing the danger of cannulating either one of these vessels, I raised the patient's arm to expose the axillary artery, which I used as the cannulation site. The aortic valve replacement was successfully performed."⁶ Bruce Lytle expanded this idea and refined the process of cannulating the subclavian artery for this problem. Substantial changes to a surgical intervention are reviewed by the Institutional Review Board (IRB), funded through academic sources, and described in new academic publications and presentations. The surgical community generally shares new methods without recovering royalties for the benefit of patients, even though novel surgical methods can be patented if desired.⁷

Determining the value

Value is the subjective relationship between the perceived benefit and perceived cost of a product or service.

$$\text{Value} = \frac{\text{perceived benefit}}{\text{perceived cost}}$$

As physicians, we are constantly assigning value to our therapies as a means of deciding how to provide medical care. We define the value of a given therapeutic intervention as the potential benefit to the patient in relation to the potential risk. Based on the risk-benefit ratio, we decide to proceed with or abandon a given therapy. Similarly, as surgeons we define the value of a surgical innovation as the potential benefit to the patient in relation to the potential risk. Based on the risk-benefit ratio, we decide to adopt or not adopt an innovation. In today's healthcare arena, before any novel surgical device is even available for use at the patient's bedside, its commercial value must be demonstrated. The commercial return on a device must outweigh its development risks in order to have a realistic chance of having the device available for patient use. To understand the value of an innovation, it is important to understand the perceived benefit the innovation has on (1) patient care, (2) technology, and (3) commercial impact (Box 33.1). We will review some of the terms used to describe an innovation's perceived benefit in these arenas.

The impact an innovation has on *patient care* can be described as revolutionary or incremental. A *revolutionary innovation* has a significant impact on patient care where an *incremental innovation* has a smaller effect. Consider the revolutionary impact of the endograft for repair of abdominal aortic aneurysms (AAA). The technique of using

BOX 33.1 Determining the value of an innovation

Impact on patient care

- **Revolutionary innovation:** significant impact on patient care, e.g. endovascular repair of AAA
- **Incremental innovation:** small effect on patient care, e.g., reiteration of laparoscopic dissector

Impact on technology

- **Enabling innovation:** serves as a platform for further developments within a field, e.g., liposuction
- **Refining innovation:** marginally improves upon available technology, does not lead to significant technology change, e.g., ultrasound and power-assisted liposuction

Impact on market share

- **Disruptive innovation:** supersedes industry leaders and takes over their market share, e.g., percutaneous transluminal angioplasty for interventional cardiology
- **Sustaining technology:** an improvement, usually by an industry lead, to maintain growth in the market, e.g., cardiac stent for interventional cardiology

a transfemoral intraluminal graft for repair of AAA was first published by Balko and associates in 1986, the first published human experience was by Parodi in 1991, and the first device manufactured was designed by Harrison M. Lazarus and developed by Endovascular Technologies Company.⁸⁻¹⁰ In September 1999, two devices were granted FDA approval for marketing. Now endovascular repair of AAA offers shorter hospital stays, decreased operative mortality and morbidity and an undisputed advantage to patients with multiple or significant comorbidities. On the other hand, consider the reiterations of multiple laparoscopic dissectors. These instruments have been developed in the attempt to improve laparoscopic dissection, but none with a significant impact on patient outcomes or care.

The impact an innovation has on *technology* can be defined as enabling or refining. An *enabling technology* is an innovation that serves as a platform for further developments within a field. In 1976, the Fischers introduced the modern era of liposuction, which is now one of the most commonly performed cosmetic surgery procedures.¹¹ This innovation has served as a platform for many further developments including ultrasound and power-assisted liposuction. Both ultrasound and power-assisted liposuction represent refining technologies. A *refining technology* is an innovation that marginally improves upon available technology and does not lead to a significant technology change.

Finally, to help describe the *commercial impact* of an innovation, the market-based terms “disruptive technology” and “sustaining technology” are used (Fig. 33.1). A *disruptive technology* is an innovation that supersedes industry leaders and takes over their market share. When disruptive technologies are introduced they are often inferior to the existing leading device and ignored by the incumbent industry leader. In surgery, the device’s inferiority is usually secondary to the device’s learning curve, lack of safety information, and inferior technology. However, as clinicians learn to use the device, as its safety profile expands and as the technology improves, its market share surpasses that of its leading competitor. The

“industry leader” can be applied to the corporation that produces the leading technology, or more broadly the subspecialty that uses the technology. For example, when percutaneous transluminal balloon angioplasty was introduced, its safety profile was not well understood and it was inferior to open coronary artery bypass. Over time, it proved to be a disruptive technology that shifted the market share of patients away from cardiothoracic surgeons (the incumbent industry leaders) to interventional cardiologists. The coronary stent, on the other hand, was a *sustaining technology*. A sustaining technology change is an improvement, usually made by the current industry leader, to maintain growth in the market. The technology can still be enabling (leading to further technology changes) or revolutionary (leading to significant improvements in patient care) but by definition it is not disruptive to market forces. In this case, the coronary stent led to further technologic advancement and improved patient outcomes but did not supersede industrial or clinical leaders. The interventional cardiologist used this technology to maintain their growth in the market.¹

Generally, the larger the perceived benefit of an innovation, the larger the potential for financial return; however, there

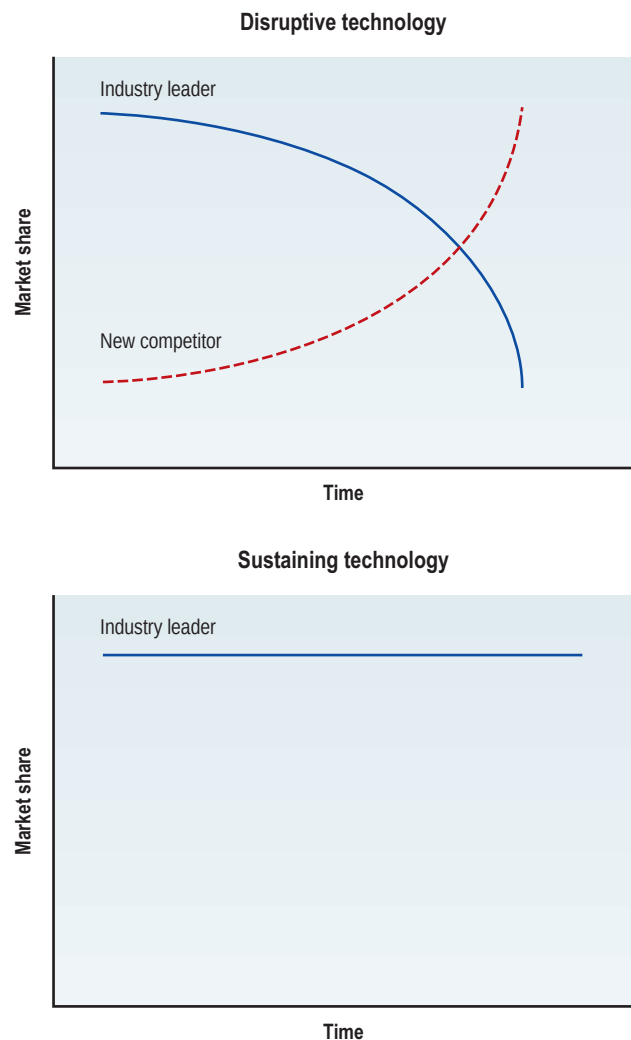


Fig. 33.1 Disruptive versus sustaining technology change.

also tends to be more risk involved in all stages of its development. With a revolutionary innovation, there is significant risk in developing the unproven technology, a riskier FDA approval pathway usually requiring pre-market approval, and more resources needed to create a large and experienced development team that can handle the challenges involved in developing a revolutionary technology. A revolutionary innovation, such as the endograft for AAA repair, will also have a large patient impact and large potential market that will justify the increased resources and risk required to develop the device. An incremental innovation, such as the “bullet” endoscopic dissector, has a smaller patient impact and ultimately less potential revenue. To justify its value, there must be less risk and resources involved in its development. Indeed there is less risk in the technologic feasibility of incremental technologies because they generally rely on proven technologies, the FDA regulatory pathway generally falls in a “510(k) pathway”, with faster approval based on predicate devices, and the development team can be a small group of focused individuals. It is important to understand what general category a new innovation falls in so that the risks and subsequently expected benefits can generally be understood.

Funding

An innovative idea develops from concept, to product, to patient use in a stepwise manner. As each milestone is met, the innovation builds value and reduces risk (Fig. 33.2). Funding throughout this process is acquired based on progress towards building value. The initial smaller investment used to prove the innovative concept is termed *seed money*. This smaller investment is generally \$50 000–\$500 000 and can come from a variety of sources: friends and family, angel investors, device company grants, small business innovation research (SBIR) and technology transfer (STTR) grants. Angel investments come from affluent individuals or a group of individuals, often with industry expertise, usually in exchange for ownership equity in the company. Angel investments in

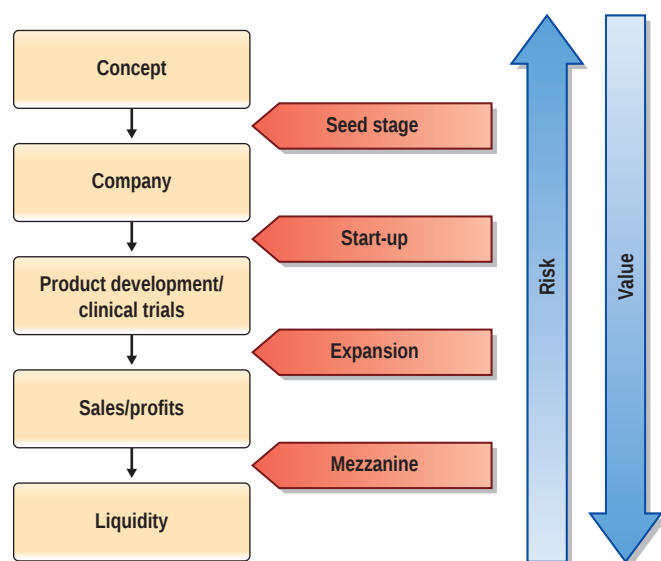


Fig. 33.2 Stages of funding.

2009 were estimated at \$17.6 billion from 259 480 active investors, with a total of 57 225 entrepreneurial ventures receiving angel funding. Healthcare services and medical devices and equipment accounted for 17% of the investments second only to software, which accounted for 19%.¹² By 2013 angel investments had increased to \$24.8 billion with over 298 000 investors compared to \$29.6 billion from venture capital.¹³ Small business technology transfer grants (STTR) reserve a specific percentage of federal R&D funding for partnerships between small businesses and nonprofit research institutions. The idea is to combine the innovative ideas that tend to come out of small businesses or academic centers that lack the means to support serious R&D, with the ability of non-profit research laboratories to develop high-tech innovations. The goal of these partnerships is to transfer the technologies from the laboratory to the marketplace, with small businesses profiting from the commercialization and thus stimulating the US economy. Each year, the Department of Defense, Department of Energy, Department of Health and Human Services, National Aeronautics and Space Administration, and the National Science Foundation are required by STTR to reserve a portion of the R&D funds towards these partnerships.

Larger investments can come from venture or corporate funding. Venture capital funds pool together investments from institutional investors and high net worth individuals. These investors become limited third party investors in the venture fund. The fund then invests in novel technologies that have the potential to generate high commercial returns at the expense of risks too high for the standard capital markets. In exchange for the high risk, venture capital funds buy a significant amount of control and ownership of the company. To ensure realization of the high risk investments, firms look for companies with an innovative technology with the potential for rapid growth with a well-developed business model, impressive management team, and markets valued at greater than \$500 million.

Venture capital is offered in stages, the funding stages parallel the growth of the company. As the new enterprise moves from concept, to company, to product, and finally acquisition, buyout or IPO it gains value and sheds risk. Venture capitalists require a detailed analysis of the development pathway with a focus on reducing risk and building value at critical growth milestones. Examples of critical milestones are securing IP, building a working prototype, successful animal testing, FDA approval and first-in-man use. Paralleling each of these growth milestones are funding benchmarks. The first funding benchmark is the seed stage; as discussed above, this can come from friends and family or angel investors. Many venture capital funds may not invest at the seed stage because the risks are very high and the concept has not been fully realized at this point. The second benchmark is known as start-up stage where the venture is ready to launch; these funds are required for company development, marketing, and product development. The third benchmark, which can be further divided into several rounds, is the expansion stage. Funds here are used for manufacturing, sales, and getting a company to a stage where it starts to turn profits. Often the final financing round is the mezzanine or bridge round which is prior to the final acquisition, buyout, or IPO. In this stage, short-term debt is usually used to support growth opportunities while preparing for an acquisition, a buyout or an IPO.

The first round of external funds is generally called “Series A” and the second round “Series B”. The investment vehicle is generally “Series A Preferred Stock” or “Series B Preferred”. This is preferred equity share in the company, meaning in exchange for their investment, the venture capital (VC) group will have first right to dividends in the case of success and liquidated assets in the case of failure. The equity share in each round is determined by the value of the company at that stage or the “pre-money valuation” in relation to the investment of the VC firm.

Intellectual property

The US Patent and Trademark Office (USPTO) issues several different types of patent documents covering different types of subject matter. Medical devices are most often protected by *utility patents*. Approximately 90% of the patent documents issued by the USPTO in recent years have been utility patents. Utility patents protect any new invention or functional improvements on existing inventions. This can be to a product, machine, a process, a method of making things, or composition of matter. A patent does not grant the *right to use* or sell an invention, rather it grants the *right to exclude* others from making, using, selling, offering for sale, or importing the invention in the United States for up to 20 years from the date of patent application filing. Thus, if an inventor takes a patented laparoscopic grasper and adds a design to make it more ergonomic, and then obtains a new patent on that improvement, he or she can exclude others from using their improvement. However, the new inventor needs the permission of the original laparoscopic grasper to manufacture theirs.

To be considered for patent, an invention must be novel, unobvious, and useful. To be novel, the invention cannot have been known or used by others or even described in a printed publication. Specifically, a US patent cannot be obtained after 1 year from the time an invention has been revealed through public use or publication. In many countries, the 1 year grace period is not granted. Thus, inventors in the academic environment should obtain intellectual property prior to publishing their work and surgeon inventors should likewise obtain intellectual property prior to public use. The invention must also be unobvious to those involved in the relevant field. Finally, it must be useful, in the case of a surgeon innovator, it must meet a patient or surgeon need.

To make sure an invention or idea is novel, the surgeon innovator can search the literature and the USPTO database. One can begin by using keyword searches to find a similar device on any publically available search engines.^{14,15} Once the closest device or invention is found, the existing patent should be intimately explored to understand which aspects of the innovation are protected and which are not.

There are three main parts of a patent: the figures, the written specifications, and the claims. The patent figures or drawings are required of almost all utility patents. The drawings must show every feature of the invention specified in the claims, and are required by the USPTO rules to be in a particular form. The written specifications are a written description of the invention, how to make it, and how to use it. The USPTO states that the specifications should be, “in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention”. Finally, the claims section is used to describe the scope of protection the applicant is requesting. This section is critical and forms the bases for litigation and prosecuting infringement. Here, technical language should be used to really define the embodiments of your innovation that differentiate it from inventions that came before. In patent language, prior inventions are referred to as prior art. The claims section really defines the invention. Most patents contain about 10–20 claims, though there are some patents with only one claim and others with hundreds of claims. There are two types of claims: independent claims and dependent claims. Independent claims stand alone. Dependent claims, on the other hand, refer to another claim on which it depends, and it has to be read in conjunction with that claim to understand the scope of the claim.

A *full utility patent application* includes the figures, written specifications, and claims as detailed above. Legal counsel, specializing in intellectual property, is advisable at this stage, as the surgeon inventor usually does not have the expertise to ensure that the utility patent meets both the inventor’s and the USPTO’s expectations. Since June 8, 1995, the USPTO has offered inventors the option of filing a *provisional patent application* to provide a lower cost (\$110–220) first patent filing in the United States. A provisional patent protects an invention in its early stages. This document describes the inventions with relevant drawings, without making any claims. Once it is submitted, the USPTO files the information but does not review it until a full utility patent application is ready for review. The provisional patent is valid for a year while the inventor perfects the invention and the utility patent application. Patentability is then evaluated as though filed on the earlier provisional application filing date, however the 20-year patent term would be measured from the later nonprovisional application filing date.

While a provisional patent offers documented protection of an invention in its early stages, patents in the United States are theoretically issued to the “*first-to-invent*” as opposed to the “*first-to-file*” approach taken by other countries. It is thus very important to have adequate proof of the date of inventions through a laboratory notebook that is dated, signed, and witnessed on a regular basis. This documentation of an invention can ultimately alter a patent’s recipient. A surgeon inventor should thus carefully document all inventions, once an invention is deemed novel, unobvious, and useful; perform an initial patent search and then file a provisional patent. Beyond the provisional patent, additional counsel should be obtained. At an academic institution this counsel can be obtained through the technology licensing office.

Institutional technology transfer

In 1980, the Bayh–Dole Act enabled small businesses as well as public and nonprofit organizations, including universities, to retain intellectual property developed during the pursuit of federally sponsored research and development. Since then, there has been an explosion of new relationships between universities, industry, and the federal government. Research universities have not only developed increasingly close ties to

Table 33.1 Basic licensing terms

Issue fee	The fee paid to the licensing body for issuance of the license
Exclusivity	A stipulation guaranteeing that no other group may license the technology for the term of the license
Term	The length of a license
Field of use	Granted use of the patent in specific fields, i.e., medical, industrial, educational
Licensed territory	The specific region granted to the licensee
Annual royalty payment	The annual fee for use of the license
Equity	Equity in the licensee company can be granted as part of the payment for a license
Earned royalty	A percentage of the revenues from products that rely on the licensed patent, paid to the licensing body
Sublicensing fee	The fee paid to the licensing body, if the licensee sublicenses

industry, but through licensing and other forms of technology transfer, universities have become an important force in the development of technology which has ultimately contributed significantly to local regional economic development.^{16–19} In the last two decades, institutional prestige for research universities has been increasingly defined in terms of commercial success, in addition to academic sciences.¹⁸

Most universities have created technology-licensing offices (TLO) to manage their patent portfolios. Surgeon innovators should become familiar with the intellectual property (IP) policies of their specific institution. Most universities have an employee contract that claims IP on any invention created with university resources. Under the Bayh–Dole Act, however, universities are also required to share a portion of new technology revenues with the inventor. The surgeon innovator thus generally begins the process of invention with disclosure of the invention to the TLO. The TLO then evaluates the technology and almost invariably chooses to retain the intellectual property. At this point, depending on the competencies and culture of the TLO, an active or passive role is taken to market a technology to industry and potential developers with the initial goal of understanding the invention's true value. Once the technology and its financial potential are understood, again depending on the culture of the TLO, various steps are taken to develop and license the technology. A fair opportunity to license the technology is generally given to the inventor. There is a huge spectrum of licensing agreements and stipulations that can or cannot be included in a licensing agreement. Some general licensing terms are outlined in Table 33.1.

FDA regulatory approval process

In the United States, medical devices are regulated by the Center for Devices and Radiological Health (CDRH), a branch of the FDA. The CDRH is responsible for promoting and protecting the public health by making safe and effective

Table 33.2 Approval pathways

Device classification	FDA regulatory approval process	Examples
Class I	Exemption: subject to general controls	Hand-held surgical instruments
Class II	510(k) pre-market notification: demonstrates equivalency to class I or class II devices with existing 510(k) approval	Suture materials
Class III	Pre-market approval (PMA): extensive data with preclinical studies and human clinical trials	Breast implants

medical devices available in a timely manner. To determine the safety and efficacy of a medical device, the CDRH has developed three main approval pathways: exemption, 510(k) pre-market notification, and pre-market approval application (PMA) (Table 33.2). The approval pathway is determined by the degree of risk associated with the device and the extent to which it poses new safety and efficacy concerns. Devices are also classified according to their perceived risk and the extent of control needed to ensure safety and effectiveness with a 3-tiered system: class I, class II, or class III. Regulatory control increases from class I to class III.

In general, device class loosely correlates with corresponding FDA approval pathways. Most class I devices are exempt from pre-market notification (PMN) or pre-market approval (PMA); most class II devices require pre-market notification 510(k); and most class III devices require pre-market approval. Class I devices are considered the lowest risk devices. They are subject to general controls. General controls are published standards regarding labeling, manufacturing, pre-market surveillance, and reporting. Devices are placed in this class when general controls alone are sufficient to assure safety and efficacy. Examples of class I devices are hand-held surgical instruments. A total of 47% of medical devices fall under this category and 95% of class I devices are exempt from pre-market notification (PMN) and 510(k) FDA approval pathways.²⁰

Class II devices are higher-risk devices. General controls alone are insufficient to provide assurance of safety and effectiveness. There is, however, enough information available to ensure safety and efficacy with special controls including performance standards, design controls, and post-market surveillance. Most medical devices are considered class II devices. Examples of class II devices include: powered wheelchairs, surgical drapes, surgical needles and suture material, and some pregnancy-test kits. A total of 43% of medical devices fall under this category. Approval of most class II devices requires pre-market notification 510(k). There are about 60 generic class II devices that are exempt from pre-market notification, as long as they meet the requirements of General Controls and Special Controls.

Class I and II devices that require more than General and Special Controls require pre-market review by the FDA with PMN or 510(k). Under 510(k), a manufacturer must

demonstrate that a medical device is substantially equivalent in intended use, technology, safety and efficacy to: (1) a class I or II device with existing 510(k) approval or (2) a device marketed prior to the Medical Device Amendments of 1976, giving it “grandfather marketing” status. One can search the FDA’s 510(k) database for devices already on the market or with grandfather marketing status.²¹ Once a PMN is submitted, the FDA has 90 days to respond. If the FDA agrees that the device is “substantially equivalent”, the manufacturer can market the device. The FDA, on the other hand, can require further data or determine the device is not substantially equivalent and re-classify the device as a class III device.

Class III devices pose the highest potential risk. These devices usually sustain or support life, are implanted, or present significant risk of illness or injury. Furthermore, they have a new intended use or technology that is not equivalent to a prior device. Given the potential safety concerns of class III devices, general and special controls alone will not provide enough assurance of safety and effectiveness. Examples include implantable pacemakers and breast implants. A total of 10% of medical devices fall under this category and these devices will usually require pre-market approval (PMA) from the FDA before they can be legally marketed. The PMA application is significantly more involved than the 510(k). Pre-market approval requires extensive data with preclinical studies, human clinical trials, and a full description of the device, including the details of manufacturing and labeling. Once a PMA is submitted, the FDA has 180 days to perform a detailed review. The FDA can grant the PMA, require more data, deny the claim, or accept with the requirement of post-market surveillance. Any substantial change to a PMN or PMA device requires new clearance.

Clinical testing of an unapproved device that poses a significant risk, or approved devices used for a purpose distinct from its approved indication, requires FDA approval in the form of an Investigational Device Exemption (IDE). The IDE application includes information of the device and the proposed study protocol.²² Both IRBs and the FDA can make the determination of whether a device will require an IDE. If an IRB determines that the device’s risk is not significant, FDA notification is not required and the IRB will oversee the trials. If the request for determination is initially submitted to the FDA, the result is binding.²² The applications and approval leading to *first clinical use* are important, because first clinical use is a key milestone for a new device company. In many cases, if a company fails to reach this milestone within a reasonable amount of time, its funding and viability will be threatened. FDA approval to initiate clinical studies in the United States is estimated to take 3–6 months, with review by IRBs adding an additional 3–6 months. Because of this time delay, many companies choose to perform their initial clinical testing outside the United States. When initial clinical testing is performed within the United States, only about one quarter of the trials are performed at academic institutions, largely attributed to bureaucracy associated with IRBs and contract negotiations at large academic institutions.²³

Conflict of interest

There is an obvious conflict of interest when a surgeon also becomes an innovator of surgical devices. The surgeon

innovator serves to benefit from the rewards of both improved patient care and financial gains as the inventor and possible developer of a given innovation. However, to help bring an invention to the bedside, the clinical inventor often becomes integrally involved in designing and developing the innovation, performing the majority of early animal studies, and eventually taking a leadership role and holding an equity position in the company developing the device. These conflicts of interest must be addressed to ensure patient safety.

There is no one comprehensive regulatory process to address all the conflicts of interest present in the process of surgical innovation. However, there are some processes that help assure third party checks and balances in human trials. Studies required for PMA approval are typically large multicenter randomized trials. The study’s sponsor typically must utilize a contract research organization (CRO), core laboratories, a data safety monitoring board (DSMB), and an executive committee, to help resolve potential conflicts of interest. The CRO helps recruit, qualify, and audit sites. Core laboratories evaluate primary data in a blinded manner. The DSMB is composed of a group of senior clinical investigators and statisticians with no other involvement in the study. They review the data at specified intervals with a mandate to stop or modify the study if harm to study participants, including an obvious benefit in one arm of the study, becomes evident. Ultimately, it is incumbent on the surgeon innovator to advance the technology they feel may benefit their patients. To do so, he/she should try to separate themselves, as much as feasible, from activities where financial gain will bias objective analysis. To help identify and avoid conflicts of interest, the surgeon innovator should also provide colleagues and patients with full disclosure of industry relationships.

Innovations in plastic surgery

Innovation in plastic surgery continues to advance our field. There is a large list of recent innovations that spans every field within plastic surgery. The impact of the various new technologies is as diverse as the technologies themselves. Negative pressure wound therapy (NPWT) was a *revolutionary innovation* in its impact in wound care and has proven to be a *disruptive technology* in its commercial impact. Acellular dermal matrix (ACM) is being used in more and more applications within plastic surgery and may become a *disruptive technology* that replaces prior synthetic or living tissue substitutes. Finally, liposuction was an *enabling technology* that served as a platform for further *refining technologies*, including noninvasive body sculpting. This small sampling of recent innovations is discussed below and we briefly touch on the spectrum of their impact on patient care, the market, and further innovation.

Negative pressure wound therapy

In the late 1980s, Drs. Louis Argenta, MD and Michael Morykwas, PhD, both professors of plastic surgery at the University of Wake Forest, developed an innovative approach to the treatment of acute and chronic wounds through the use of sub-atmospheric pressure known today as negative pressure wound therapy (NPWT). In 1993, a partnership between KCI

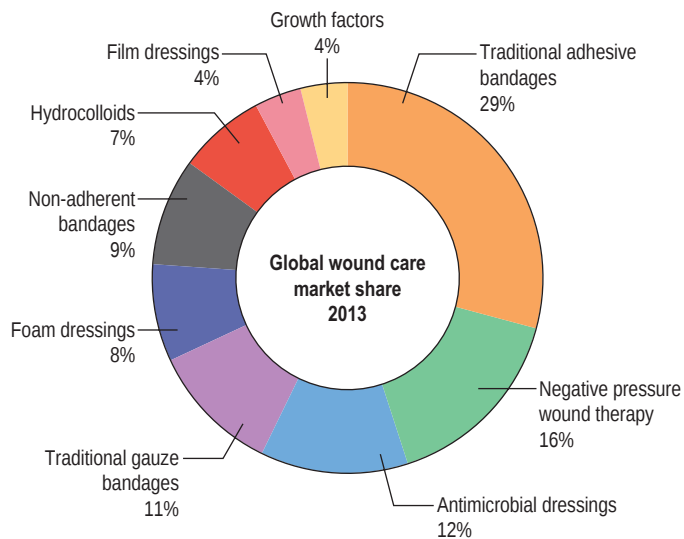


Fig. 33.3 Global wound care market share, 2013.

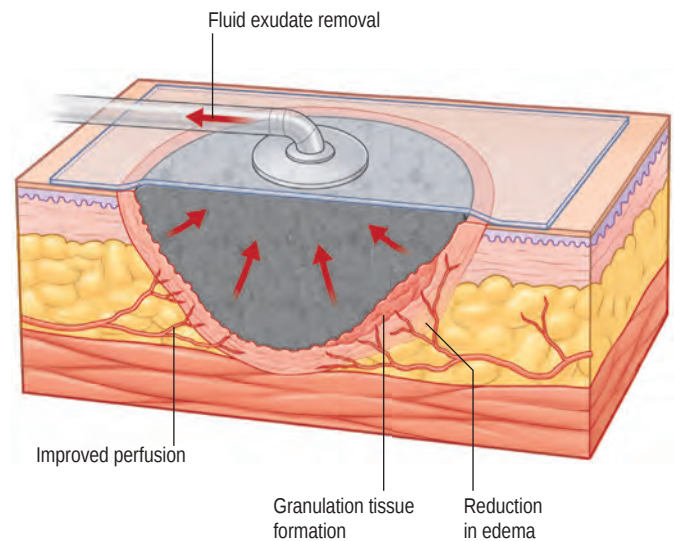


Fig. 33.4 Negative pressure wound therapy.

and Wake Forest allowed KCI to commercialize what became KCI's proprietary VAC therapy system. Two years later, the system was approved by the FDA and launched. Then in 2000, KCI received approval for Medicare Part B reimbursement for VAC therapy, making it available to elderly and disabled homecare patients in the United States. This *revolutionary technology* has changed the way many acute and chronic wounds are treated. Today, KCI's wound VAC has served more than 9 million patients worldwide. Its commercial impact continues to be an example of a *disruptive technology*. In 2013, NPWT had the second largest share of the wound care market, second only to traditional adhesive bandages²⁴ (Fig. 33.3), meaning many of the prior industry leaders have been displaced by this new competitor.

NPWT, also referred to as vacuum-assisted wound closure, applies continuous intermittent sub-atmospheric pressure to the surface of a wound (Fig. 33.4). Several potential mechanisms have been proposed to explain how NPWT works. One proposed mechanism is that it reduces wound edema. By removing this transudative and exudative fluid, NPWT improves oxygenation to cells. NPWT also diminishes mediators of the inflammatory response. In humans, it has been shown to decrease matrix metalloproteinase. MMPs inhibit angiogenesis by generating inhibitors such as angiostatin and endostatin.²⁵ NPWT is also thought to act via mechanotransduction; the conversion of mechanical stimulus into chemical activity. *In vitro*, the mechanical deformation increases human fibroblast growth and migration and in animal models of wound closure, the mechanical deformation correlates to increased collagen organization and expression of vascular endothelial growth factor and fibroblast growth factor.^{26,27} These modifications of a wound's microenvironment make it more conducive to wound healing.

NPWT is being used to treat a spectrum of wounds including acute wounds, diabetic wounds, open abdominal and sternal wounds, pressure ulcers, and in conjunction with grafts and flaps. However, high quality evidence supports its use over conventional techniques, most clearly in the setting of diabetic foot wounds. When compared with wet to dry dressing changes in diabetic foot ulcers, NPWT reduces time

to wound closure, length of hospitalization, complication rates, and costs.²⁸⁻³⁵

There is a lack of high level or consistent evidence, however, to support its superiority when compared with traditional moist saline dressings in non-diabetic wounds. In these settings, the more clear advantage was that NPWT met additional surgeon-user needs including decreased number of dressing changes and ease of use. In the traumatic setting, there are observational studies that show its efficacy is comparable, but not superior, to standard dressing changes,³⁶ however the frequently cited advantages, in the trauma population, are: ease of application, decreased number of dressing changes, and reduction in the complexity of subsequent reconstructive surgery.^{37,38} In the treatment of pressure ulcers, no statistically significant differences have been shown in wound surface area, however the cited advantages have been improved patient comfort and less labor intensity.^{39,40}

High-level evidence showing the superiority of NPWT compared with traditional moist saline dressings is still lacking, however it is clear that NPWT meets very specific needs of the surgeon or end user. NPWT is easy to use; it decreases the number of dressing changes for both the patient and the medical caregiver and ultimately prepares the wound for surgical closure by tertiary intention. By understanding and meeting the needs of the surgical community, the plastic surgeon and engineer that developed NPWT changed the armamentarium of the general surgeon's approach to the open abdomen, the cardiothoracic surgeon's approach to post-sternotomy mediastinitis, the vascular surgeon's approach to groin wounds and, ultimately, the plastic surgeon's approach to all of these wounds as well as graft and flap reconstruction. The clinical adoption, despite lack of high level and consistent data, makes it a *revolutionary technology* that translates into a commercially *disruptive technology* (see Fig. 33.3).

Acellular dermal matrix

In recent years, acellular dermal matrix (ADM) is emerging as a *disruptive technology* in both reconstructive and aesthetic

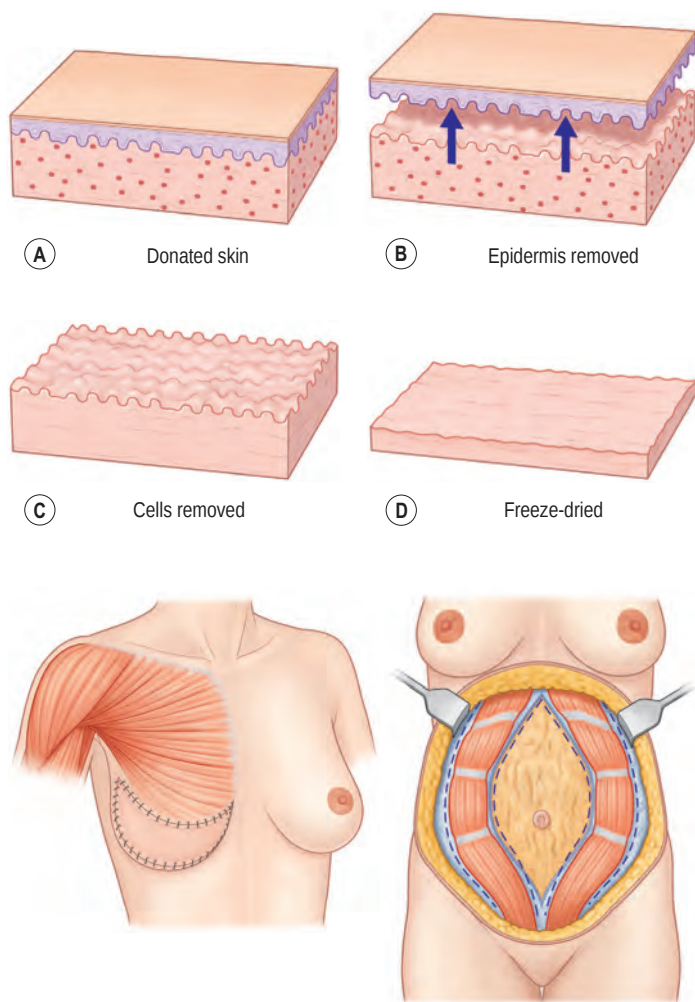


Fig. 33.5 Acellular dermal matrix.

surgery. ADM is a dermal graft in which the dermis is separated from the epidermis and all cellular elements, to avoid tissue rejection and graft failure (Fig. 33.5). The dermal matrix then acts as a scaffold that permits tissue regeneration with revascularization and repopulation with fibroblasts. The ADM is thought to incorporate into surrounding tissue and eventually be replaced with host collagen.⁴¹

Its use has been described in the burn literature for over 20 years; initially as a substitute, and now as a complement to skin grafting. In the field of breast surgery, ADM was first described in revision aesthetic cases to address rippling and symmastia.^{42,43} In 2005 it was introduced in reconstructive breast surgery as a tool for direct-to-implant reconstructions.⁴⁴ In 2007 its use in two-stage breast reconstruction with a tissue expander was described.⁴⁵ ADM is used to provide additional coverage of implant-based reconstructions, support for faster inferior pole expansion, as well as assistance with precise placement of the inframammary fold.^{46,47} Overall, studies still conflict on its risk profile for postoperative breast complications. A retrospective analysis of 415 immediate implant-based breast reconstructions showed that ADM is associated with high rates of postoperative seromas and infection.⁴⁸ ADMs, however, are used in over 60% of implant-based breast reconstructions. In this market ADM has disrupted the prior

ADM: a disruptive innovation in implant-based breast reconstruction

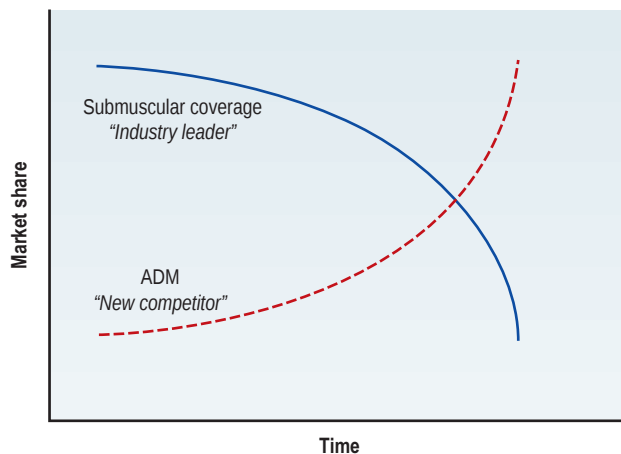


Fig. 33.6 ADM is emerging as a disruptive innovation in implant-based breast reconstruction.

“leader” which was implant-based reconstruction with partial or total muscle coverage (Fig. 33.6). Similar to NPWT, ADM has been adopted prior to data to support its superiority to traditional methods. Its adoption may be attributed to ease of use and meeting surgeon needs that include a quick way to reconstruct the inframammary fold.

ADM is also largely replacing the use of synthetic meshes in contaminated abdominal wall defects. These bioprostheses are thought to incorporate into contaminated tissue without becoming infected.⁴⁹ This is an important competitive advantage when compared to synthetic mesh, which is contraindicated in this setting. There still remains a question of the longevity of mechanical integrity ADM provides in abdominal wall reconstruction. However, because ADM has met the need for a large fascial substitute that can be used in the setting of a contaminated wound, many plastic surgeons quickly adopted this new technology, despite these unanswered questions. Interestingly, by embracing ADM-based abdominal wall reconstruction, plastic surgeons are expanding their role among general surgeons in this arena.

Like other disruptive technologies, this emerging technology lacks long-term follow-up, familiarity, and a complete safety profile. However, it is a soft-tissue substitute that needs not be harvested, thus fills a principle need of the reconstructive surgeon. This technology may thus go on to expand its indications, supersede other synthetic technologies, and replace more invasive reconstructive options of the present.

Noninvasive body contouring

The push towards noninvasive medical interventions is an important force driving the patient-consumer market for medical intervention. At its inception over three decades ago, liposuction itself was a large step in a less invasive form of body contouring compared with traditional surgical approaches. The introduction of liposuction, like other *enabling technologies*, served as a platform for the continued introduction of *refining innovations*. The Fischers first introduced sharp suction techniques for fat removal in 1974. Illouz then refined the technique with the introduction of high power negative pressure suction connected to blunt tip cannulas as well as the

development of the “wet technique” used for hydrodissection to assist with fat removal.⁵⁰ In the 1980s, Dr. Jeffrey Klein introduced the tumescent technique that had an important impact on the safety and efficacy of liposuction. The high volumes of diluted lidocaine and epinephrine decreased the need for general anesthesia and minimized blood loss.⁵¹

To address surgeon fatigue and improve effectiveness, especially in more fibrous areas, several *refining innovations* have been introduced, none of which have made a significant change in this field.⁵² Ultrasound-assisted liposuction (UAL) was developed by Zocchi in the 1980s. Ultrasonic waves were introduced to rupture adipocytes creating microcavitations of liquefied fat. Controversy exists as to whether UAL reduces complications or improves efficacy when compared with traditional techniques.^{53,54} Similarly, power and laser-assisted lipolysis were refinements to traditional liposuction that have not shown significant differences in clinical outcomes.⁵² Focused ultrasound body contouring is a recent innovation that introduces a potentially new frontier in body contouring that may or may not prove to be efficacious. This technology uses focused ultrasound energy delivered through a handheld probe (Fig. 33.7). The ultrasonic waves are focused in the subcutaneous fat, causing permanent disruption of fat cells with the aim of not damaging the epidermis, dermis, or underlying tissues and organs. The disrupted adipocytes are then supposed to be metabolized by the liver. The procedure is a change from prior refinements, as it requires no incisions or injections. This technology is not FDA approved for use in the United States. Small preliminary clinical trials and use outside of the United States have demonstrated safe and effective treatment in small areas.^{55–57} Since its inception in the 1970s, liposuction has proven to be an enabling technology that continues to serve as a platform for numerous refining technologies.

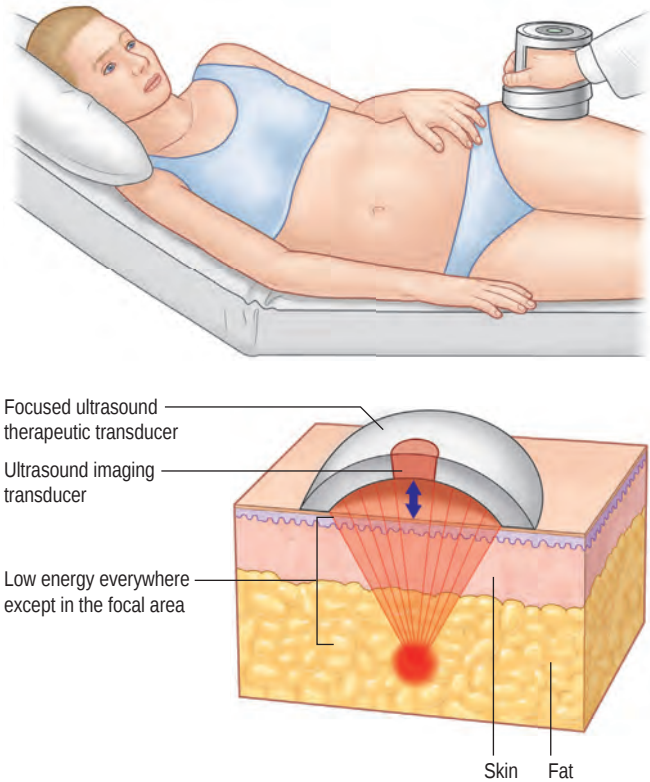


Fig. 33.7 Noninvasive body contouring.



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Robotics in plastic surgery

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SYNOPSIS

- This chapter details the recent history of innovations in robotic plastic surgery. Clinical applications are described and discussed. Future perspectives for the growth and dissemination of this field are outlined.
- Robotic technology is the next step in the evolution of minimally invasive techniques, adding enhanced precision and visualization, augmenting the capabilities of plastic surgeons, and aiding in achieving more precise interventions.
- The robotic interface has provided the necessary exposure and picture clarity through high-resolution, three-dimensional optics and the precision instrumentation to accomplish minimally invasive muscle harvest, including microvascular pedicle dissection, without additional skin incisions.
- With improved visualization, elimination of physiologic tremor, motion scaling, and decreased fatigue, the surgical robot has emerged as a potentially useful tool in microvascular, microlymphatic and microneural surgery.
- Trans-oral robotic surgery (TORS) has been shown to be a reasonable alternative to chemoradiation treatment for many tumors of the hypopharynx. Reconstructive techniques using the robot to access oropharyngeal anatomy has allowed more of these defects to be reconstructed without splitting the mandible and thus have extended the indications for TORS.
- The intrinsic features of robots, including superhuman precision, high definition, three-dimensional optics and minimally invasive capabilities, have enabled plastic surgeons to perform minimally invasive approaches to procedures never before possible.
- The application of the robotic platform to microsurgery is growing owing to the development of new microsurgery-specific robotic instrumentation. As more microsurgeons use the robotic platform, an increasing number of manufacturers will be driven to design improved tools for microsurgical procedures.

Introduction

The word “robot” was first introduced to the English language and to science fiction in 1921 by Karel Čapek in his play

Rossum’s Universal Robots; it is a term derived from the Czech word *robota*, which means “forced labor”.¹ Since then, robots have assumed an increasingly significant role in both industry and medicine. It was the National Aeronautics and Space Administration (NASA) and the US Army who initially promoted the concept of robotics in surgery after their development of telepresence surgery (operating remotely) for use in wartime and for space applications.¹

The history of robotic surgery began with Puma 560 which was first used by the neurosurgeon Kwoh to achieve improved absolute positioning accuracy for CT-guided stereotactic brain surgery.² Three years later, Puma 560 was used by the urologist Davies to perform a transurethral resection of the prostate.³ This platform led to the development of the PROBOT, a robotic system specifically designed for transurethral resection of the prostate.⁴ At the same time, orthopedic surgeons were also taking advantage of robots’ greater precision; they developed a system that could assist in total hip arthroplasty (preparing the human femur for artificial hip replacement).⁵ The RoboDoc system (Integrated Surgical Systems, Inc., Sacramento, CA) was eventually developed and used to prepare the femoral canal for prosthesis placement; RoboDoc was the first surgical robot approved by the FDA.⁶

Based on the promise of surgical robotics, several other systems have been researched, and then commercially developed and approved by the FDA to integrate various fields. These included the Automated Endoscopic System for Optimal Positioning (AESOP) system (Computer Motion Inc., Santa Barbara, CA), a voice-activated robotic endoscope, and the comprehensive surgical robotic systems, Zeus (Computer Motion Inc., Santa Barbara, CA) followed by da Vinci (Intuitive Surgical Inc., Mountain View, CA).⁷

The da Vinci platform is a so-called “master-slave” system, meaning that robotic arms are controlled remotely from a console in which the surgeon sits and performs the surgery. The da Vinci system is composed of three components: a vision tower that holds a dual light source and dual 3-chip cameras, a master console where the operating surgeon sits,

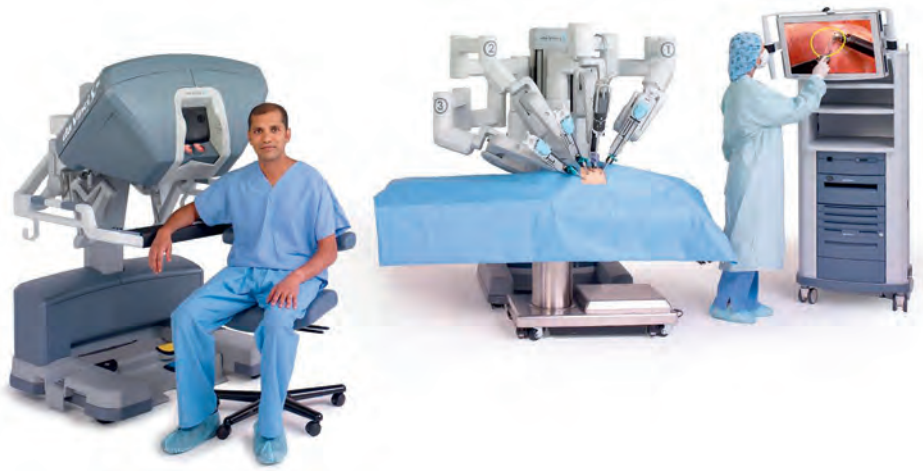


Fig. 34.1 The full da Vinci Si HD surgical system (from right to left): an imaging cart, a mobile cart with four articulated arms, and a console for the surgeon to control the robot arm (reprinted with permission from Intuitive Surgical, Sunnyvale, CA).

and a moveable, patient-side cart, where two instrument arms and the camera arm are mounted⁸ (Fig. 34.1).

Robots have been used in a variety of minimally invasive surgeries, including cholecystectomies, mitral valve repairs, radical prostatectomies, reversal of tubal ligations, in addition to many gastrointestinal surgeries, nephrectomies, and kidney transplants.⁷ Advantages are many as robots were able to overcome the shortcomings of laparoscopy, and have made possible surgeries that were previously technically unfeasible. These benefits include increased dexterity, improved visualization, restoration of proper hand–eye coordination, elimination of physiologic tremors, ability to scale motions, seven degrees of freedom, and an ergonomic surgeon positioning.⁹

Robotics in plastic surgery

Inspired by the success of robotics in these other surgical specialties, the senior author (JCS) began investigating the use of robots in plastic surgery in 2003. Over the subsequent 10 years, three applications of robotics in plastic surgery were developed: (1) trans-oral robotic *reconstructive* surgery (TORRS) for head and neck reconstruction, allowing complex oropharyngeal reconstruction without dividing the lip or mandible; (2) robotic microvascular, microneural, and microlymphatic anastomoses, extending the capabilities of the human hand to “supra-human” precision; and (3) minimal access muscle harvest for an “incisionless” harvest of both the latissimus dorsi and rectus abdominis muscles. In this chapter, we present the clinical experience of robotic surgery in those areas.

Trans-oral robotic *reconstructive* surgery (TORRS) (Video 34.3 ►)

Malignant lesions of the oropharynx and base of tongue remain a prevalent and challenging entity to treat. The frequent need for debilitating surgical procedures (lip and mandible splitting) to resect such tumors has led to the use of primary chemoradiation therapy as an alternative treatment.^{10,11} However, toxicity rates following such approach were considerably high and functional status was not improved.¹² The advent of robotic surgery for minimally

invasive resection of oropharyngeal malignancies has witnessed the return of surgery as a primary treatment modality for such tumors.^{13,14} Trans-oral robotic surgery (TORS) offered the possibility of achieving loco-regional tumor control while avoiding the need for mandibulotomies and chemoradiotherapy, optimizing both oncologic and functional outcomes. The reconstructive challenge created by these minimally invasive resections is that the cylinder of the oropharynx remains almost entirely closed, severely restricting its access when attempting to inset and contour vascularized tissue. The anatomic region between the uvula and the epiglottis is particularly difficult to approach without a mandibulotomy or a wide pharyngotomy. Trans-oral robotic *reconstructive* surgery (TORRS),¹⁵ whether using free flaps, local flaps, or primary closure, allows access to this difficult anatomy to facilitate suture approximation and achieve the goals of reconstruction: preservation of a competent velopharyngeal sphincter, a watertight seal between the pharynx and neck, adequate sensation and volume in the tongue base, and optimization of the physiological function of the oropharynx and larynx.^{16,17} Set-up involves positioning the patient-side cart at about 60° from the head of the bed. A mouth retractor is used to establish the interdental opening and the endoscope and two instrument arms are passed into the mouth, converging to the target anatomy (Fig. 34.2).

The “remote center” of the instruments is the virtual, three-dimensional point around which the instruments’ pivot is placed at the level of the mouth opening to minimize movement around the teeth. Complex manipulation of tissue, including delicate suturing, can then be performed. This approach appears to be a superior option in select cases, and also holds promise in expanding the indications for minimally invasive reconstructive procedures. Combining trans-oral robotic flap inset with manual inset through the pharyngotomy defect is also possible. In these cases, however, it is important to note that a pharyngotomy is considerably smaller than the wide pharyngotomy traditionally required for accessing such tumors, since access to the upper pharynx is achieved robotically rather than through the neck. The senior author has documented the value of TORRS for challenging defects of the head and neck, and has shown both the feasibility¹⁸ and effectiveness¹⁹ of this reconstructive method. In addition, by taking this approach, plastic surgeons are able to provide a

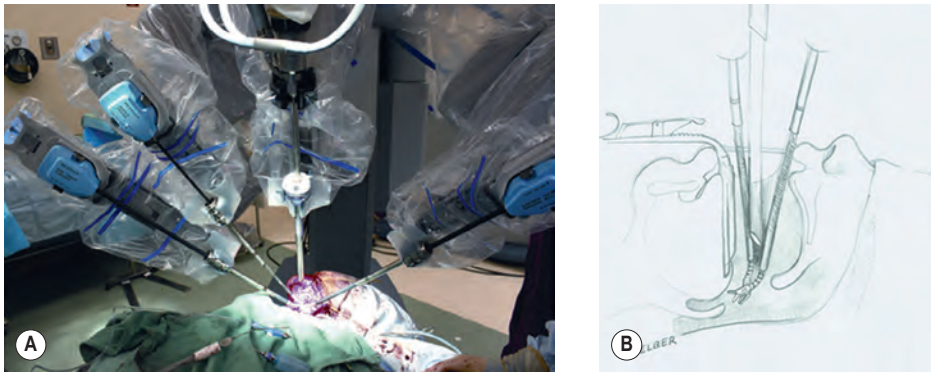


Fig. 34.2 Trans-oral robotic reconstruction requires a mouth retractor to set the interdental opening. The robotic endoscope and two robotic instrument arms are introduced through the mouth and converge on the target oropharyngeal anatomy. External view (A) and depiction of internal view (B) is shown. (From Selber JC, Sarhane KA, Ibrahim AE, Holsinger FC. Transoral robotic reconstructive surgery. *Semin Plast Surg.* 2014;28:35–38.)

reliable reconstructive support for the head and neck surgeon to robotically resect larger, deeper, and more complex tumors that would be very challenging to reconstruct through traditional methods.

Indications for TORRS application are still not completely defined. Longfield *et al.* recently proposed an algorithm for the use of TORRS based on tumor site, tumor extent, and patient-specific factors.²⁰

Robotic microsurgery (Video 34.1 ►)

One of the most promising applications of robots in plastic surgery is microsurgery. With complete tremor elimination and up to 5:1 motion scaling, the surgical robot is capable of superhuman levels of precision. In no area is this precision more important than in microsurgery. Furthermore, with its high-definition three-dimensional optics and up to 10× magnification, robots provide a nearly ideal platform for performing delicate microvascular manipulations. Robotic microsurgery was first investigated in a rat model where it showed a significantly slower time to anastomosis versus conventional microsurgery, with no difference in technical failures or patency rates.²¹ A more recent objective study compared 30 standard and 31 robot-assisted anastomoses, and showed excellent patency rates for both methods, but a significantly longer time for robotic cases.²² In contrast, Katz *et al.* showed a learning curve that resulted in a decrease of

robotic anastomotic time from 67 to 20 minutes.²³ Morita *et al.* reported a quantitative assessment of robotic versus freehand tasks in a microsurgical setting; a simulated deep and superficial surgical field was created and robot assistance was more successful for the deep microvascular tasks.²⁴

In the senior author's initial series of trans-oral robotic reconstruction of oropharyngeal defects,¹⁹ the robot was used to perform the microvascular anastomoses. The facial artery, which is the most common recipient artery, is found passing beneath the hypoglossal nerve and digastric sling, often high under the body of the mandible. If a tracheostomy and ventilator tubing is also connected, the space available to perform the anastomosis may be limited. The robot's precision and visualization in confined spaces makes it well suited for anastomoses in such cases. Similarly, Song *et al.*¹⁷ used the robot for microvascular anastomosis of a radial forearm flap (recipient vessel: facial artery) to reconstruct the defect created by resecting a tonsillar tumor (T3 N0 M0, stage III); the neck dissection was performed through a retro-auricular incision. In this type of approach, the authors also stated it is more difficult to perform the micro-anastomosis through the narrow space using a conventional microscope. Set-up for robotic microsurgery is relatively straightforward. The robotic arms are placed at about 45° above the target anatomy and in direct proximity to the external incision (Fig. 34.3) (Video 34.5 ►).

A third arm with a “fine tissue forceps” attachment serves as a stationary assistant, and the surgeon is able to toggle back

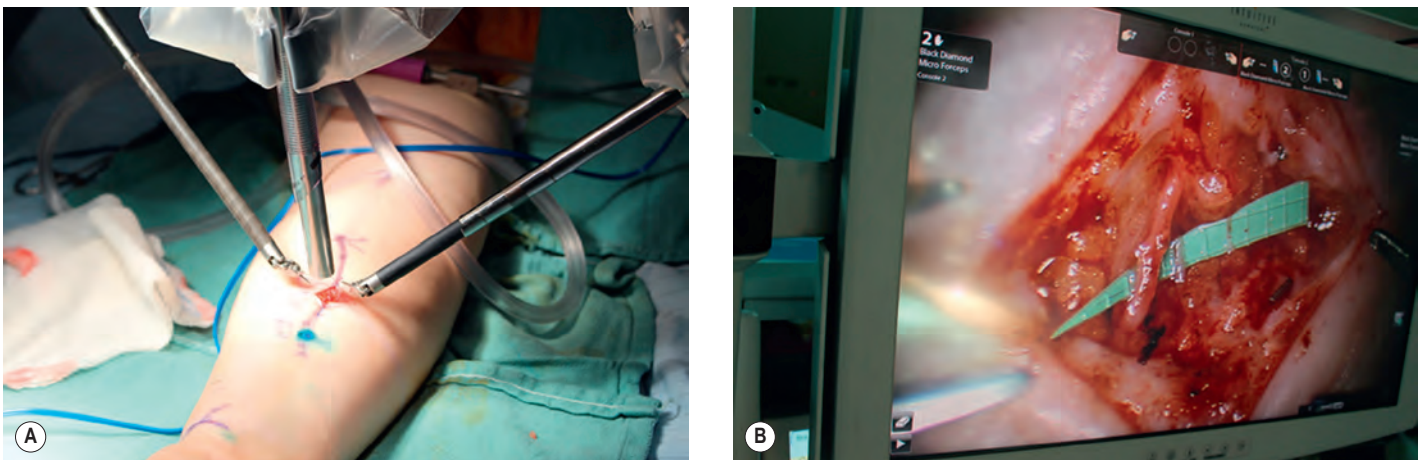


Fig. 34.3 Robotic lymphovenous bypass. The robotic camera is positioned in the middle, and the two arms are on either side of the forearm (A). Lymphovenous bypass completed (B).

and forth between arms 1 and 3, depending on which arm is being used to position the vessel, and which is being used to suture. Black Diamond Micro Needle drivers (Intuitive Surgical) replace the larger jawed needle drivers used during the inset, and a 9-0 nylon suture is used for the anastomosis.

The main highlights of robot-assisted surgery (ultra-precision and 100% tremor filtration) are currently being expanded to the field of super-microsurgery, specifically to lymphedema surgery. Lymphaticovenular bypasses are generally performed end-to-end using 11-0 or 12-0 nylon sutures on a 50- μ m needle.²⁵ These are extremely technically challenging cases, and in certain cases exceed the limits of human precision. The supra-human precision afforded by the robot can be of great benefit in this setting. The senior author has performed several lymphovenous bypass surgeries using the da Vinci platform and found it to be promising for this application. In addition, the robotic platform allows rapid transitioning of the visual system between near-infrared laser visions (when using indocyanin green to identify lymphatics) to normal bright field vision, which is a great advantage for lymphatics surgery when identifying lymphatic vessels using physiologic flow.

The advantages of robotics over endoscopy (disappearance of physiological tremor, three-dimensional vision, high definition, magnification, and superior ergonomics) have led to its use for microneural and brachial plexus surgery. Nectoux *et al.*²⁶ demonstrated the feasibility of robotic microneural repair in their experiments on fresh nerves (rat thigh sciatic nerve, pig upper limb median nerve, and human wrist median nerve, human wrist ulnar nerve, and human finger collateral nerve) using either an anatomical (epiperineural repair) or a neurotrophic technique (nerve regrowth guide). Repairs were all performed without any damaging movements. They concluded that the robot allows very safe and precise peripheral nerve repairs by counteracting physiological tremor and improving the overview of the surgical field.

These promising results allowed them to use the robot for intraneural dissection of peripheral nerve tumors.²⁷ The robotic approach permitted, in addition to a minimally invasive approach, a higher degree of precision, allowing identification of the fascicles with greater accuracy and safety.

The brachial plexus is composed of a complex web-like array of nerves and several intertwined connections, making it a very intricate anatomical environment which poses great surgical challenges. Access to the brachial plexus traditionally requires a long incision, with significant dissection, and this often results in substantial scarring and adhesions. For this reason, the traditional approach has been to treat closed injuries with watchful waiting. However, this can lead to a delay in exploration of 3 to 6 months post-injury. Although endoscopic approaches could mitigate the cost of early exploration by reducing incisional morbidity, the technique does not allow finely tuned microneural repairs. A minimally invasive approach with three-dimensional (3D) high-definition, high-magnification vision allows early exploration of the brachial plexus to diagnose the injuries and perform higher quality microneural repairs without the open incision. Facca *et al.*²⁸ have presented their experimental and clinical experience in robotic-assisted surgery of the shoulder girdle and brachial plexus. In their cadaveric studies, they were able to dissect the supraclavicular brachial plexus and adjacent anatomical structures (jugular vein, omohyoid

muscle, phrenic nerve, scalene muscles, and nerve roots from C4 to C7). A complete dissection and full exposure of the supraclavicular portion of the brachial plexus was successfully achieved. They were also able to graft a nerve segment into an artificially created gap by performing separate epi- and perineural repairs with 10-0 nylon.

Finally, it is worth noting that new directions for robotic microsurgical applications are being explored in the field of urology. These include robotic-assisted vasectomy reversal, sub-inguinal varicocelelectomy, denervation of the spermatic cord, and testicular artery re-anastomosis (in case iatrogenic injuries occur). Parekattil *et al.*²⁹ presented their experience with these techniques and concluded that the use of robotic assistance in microsurgical vasovasostomy may have benefit over conventional techniques in decreasing operative duration and significantly improving early semen analysis measures. As for robotic-assisted microsurgical subinguinal varicocelelectomy, this technique appears to be feasible, and there are potential advantages in decreasing operative duration and improving surgeon efficiency.

Robotic microvascular anastomosis is a burgeoning application whose future in microsurgery is promising. Preliminary results suggest that surgical robots could play a key role in microsurgery in the future.^{28,30-32} The current limitations of the robotic platform for microsurgery include inferior optics of the endoscope compared to the operating microscope, instruments that are clumsy compared to fine microsurgical instrumentation, and lack of haptic (sensory) feedback. Only one study has objectively assessed haptics and concluded it was not crucial to completing an accurately tied knot with a microsurgical suture.³³ Subjects tied knots and tightened them with eyes open and closed with robotic assistance. No difference in suture breakage and poor tightening was observed.³³ The senior author's experience is that microsurgery is 90% visual, and most of what we imagine we are feeling, we are actually seeing, and our brain is supplying the illusion of sensation. The 10% of haptic feedback that is real, however, is a very important component and, at this time, constitutes a barrier to robotics playing a more active role in microsurgery. In addition, the robotic endoscope is limited in both its clarity, resolution and magnification compared to the optics of more traditional operating microscopes. These differences can be overcome with better quality, fixed distance lenses fitted to the stereoscopic optical system of the robot. More delicate instruments are required which bear greater resemblance to traditional microsurgical instruments and would accommodate basic forms of haptic feedback (see below).

Robotic muscle harvest: latissimus dorsi and rectus abdominis (Videos 34.2 and 34.4)

Free and pedicled muscle flaps have been in use by plastic surgeons for a variety of applications since World War I, and remain work horses in scalp, extremity, head and neck, and breast reconstruction. Harvest of muscle flaps traditionally requires incisions that provide access to muscle origin, insertion and pedicle ranging from 20 to 40 cm in length. These donor sites are conspicuously located on the abdomen and back, and are a source of morbidity in the form of poor cosmesis, discomfort, seroma and hernia. Because of the desirability for minimally invasive harvest, endoscopic and laparoscopic techniques have been attempted, but have not

achieved broad acceptance due to technical challenges related to exposure, retraction and lack of appropriately precise instrumentation.^{34–36} The robotic interface has supplied the necessary exposure and picture clarity through high-resolution, three-dimensional optics, and the necessary precision instrumentation to accomplish both muscle and pedicle dissection. For this reason, robotic muscle harvest holds excellent promise in reducing donor-site morbidity for these common reconstructive procedures. The senior author has designed and refined the technique to harvest both the latissimus dorsi and rectus abdominis muscles.

Robotic harvest of the latissimus dorsi muscle flap was developed in a cadaver model in 2010.³⁷ It was first used clinically in 2011 in a series of 8 patients,³⁸ and has since been used in over 40 latissimus harvests at the senior author's institution. It is a safe procedure with diminished donor-site morbidity and no major complications. The approach involves a short axillary incision, or simply use of the existing mastectomy incision or sentinel lymph node incision, two additional ports, and insufflation. The entire muscle can be harvested and transposed through the small incision, and has many uses as a free and pedicled flap, including partial breast reconstruction and implant coverage, as well as free flap applications. Over the past two years, this harvest technique has been gaining popularity among breast reconstruction surgeons as it proved to be a feasible technique that allows adequate coverage of the breast providing a reliable reconstruction with hidden incisions. The technique has been performed worldwide. Its major indications include reconstruction of lateral defects following partial mastectomy, implant-based reconstruction following nipple–areola complex sparing mastectomies, and in secondary reconstruction in patients with expanders who received adjuvant radiotherapy (delayed-immediate protocol). Additionally, it can be used for chest wall deformity correction in patients with Poland syndrome.³⁹ The operative procedure is discussed in detail elsewhere.⁴⁰ A novel gasless technique using an articulated long retractor to maintain an adequate working space and enable latissimus dorsi muscle dissection (without gas insufflation) was also recently described.³⁹ In addition to improved cosmesis, the robotic approach demonstrates reduced patient discomfort, decreased seroma formation and shortened length of stay compared to the open procedure (Fig. 34.4).

Robotic harvest of the rectus abdominis muscle uses an intraperitoneal approach, avoiding violation of the anterior rectus sheath and hence decreasing the incidence of postoperative surgical site occurrences.⁴¹ The first published report of robotic rectus harvest was performed on a 30-year-old woman for a lower extremity defect.⁴² The authors observed advantages of the robotic approach, including uninhibited 3D view of the rectus muscle and the deep inferior epigastric artery (DIEA), dexterity levels similar to human hands, and a clearer image than traditional laparoscopy. Additionally, during the dissection it was noted that gravity serves to auto-retract the muscle and makes the perforators and inscriptions easier to visualize. The operative procedure is discussed in detail elsewhere.⁴³ Based on our experience, robotic harvest of the rectus muscle is a valuable option for plastic surgeons, and can be performed for many different types of reconstructions. Indications are classified according to the pedicle supplying the flap. A superiorly-based pedicled flap is used for the coverage of anterior midline chest wall and sternal defects following

oncologic resection or wound debridement. Inferiorly based flaps are used to reconstruct abdominopelvic defects where either space obliteration or visceral protection is needed: abdominoperineal resection, radical cysto-prostatectomy, pelvic exenteration, and coverage of major vessels or visceral repairs. Harvest of the muscle for free tissue transfer can also be performed robotically, and indications are primarily scalp and extremity, as in the traditional approach. We observed several key advantages associated with the robotic approach for this surgery. As outlined above, the rectus muscle is traditionally accessed through long incisions to free its origin and insertion. With the assistance of the robot, these are reduced to ports, with less risk of wound complications and improved cosmesis. Maintaining the integrity of the anterior rectus sheath resulted in a minimal incidence of hernias and bulges. Overall, less tissue violation is required, and this has resulted anecdotally in markedly reduced postoperative pain and patient discomfort, shorter length of hospital stay, and more rapid functional recovery. Finally, this procedure can easily be combined with other pelvic procedures. This is of great value to a complex, multi-disciplinary robotic surgery program where large resections are being performed without a laparotomy (Fig. 34.5).

In sum, robotic muscle harvest techniques are safe and effective, and have a place in the practice of reconstructive surgery.

Limitations of robotic surgery

Cost

Cost presents the commonly discussed obstacle to routine use of the robot in plastic surgery. The current cost of the da Vinci system is \$2.2 million and annual maintenance is \$138 000. This cost has been accepted by hospitals in anticipation of increases in patient volume and reputational benefit. The determinate of whether a robotic practice is profitable is the *contribution margin per case*. This is calculated by subtracting the cost per case from the revenue per case. For most cases, revenue from a robotic case is the same as the open procedure, fixed by the professional fee charged by the doctor and the hospital fees, based on the DRG (there are no special robotic surgical codes). For robotic procedures, OR cost may be higher due to instrumentation, staffing levels and OR time, particularly if the procedure takes longer when done robotically. On the other hand, hospital costs may decrease if minimally invasive robotic procedures are associated with shorter lengths of stay and lower complication rates. The balance of revenue and cost per procedure will determine if the robotic procedure is cost effective. In our institution (MD Anderson Cancer Center), a robotic latissimus dorsi (LD) harvest costs an additional \$800 to \$900 as compared to an open LD flap.⁴⁴ Although at first glance cost seems to be a substantial drawback for the widespread application of the robot, when considering the advantages offered in terms of decreased morbidity and hospital length of stay, robotic-assisted procedures might compare favorably to traditional approaches.⁴⁴ Prospective long-term studies are needed to objectively assess the cost-effectiveness of this new technology in terms of operative time, recovery period, hospital length of stay, and morbidity rates.

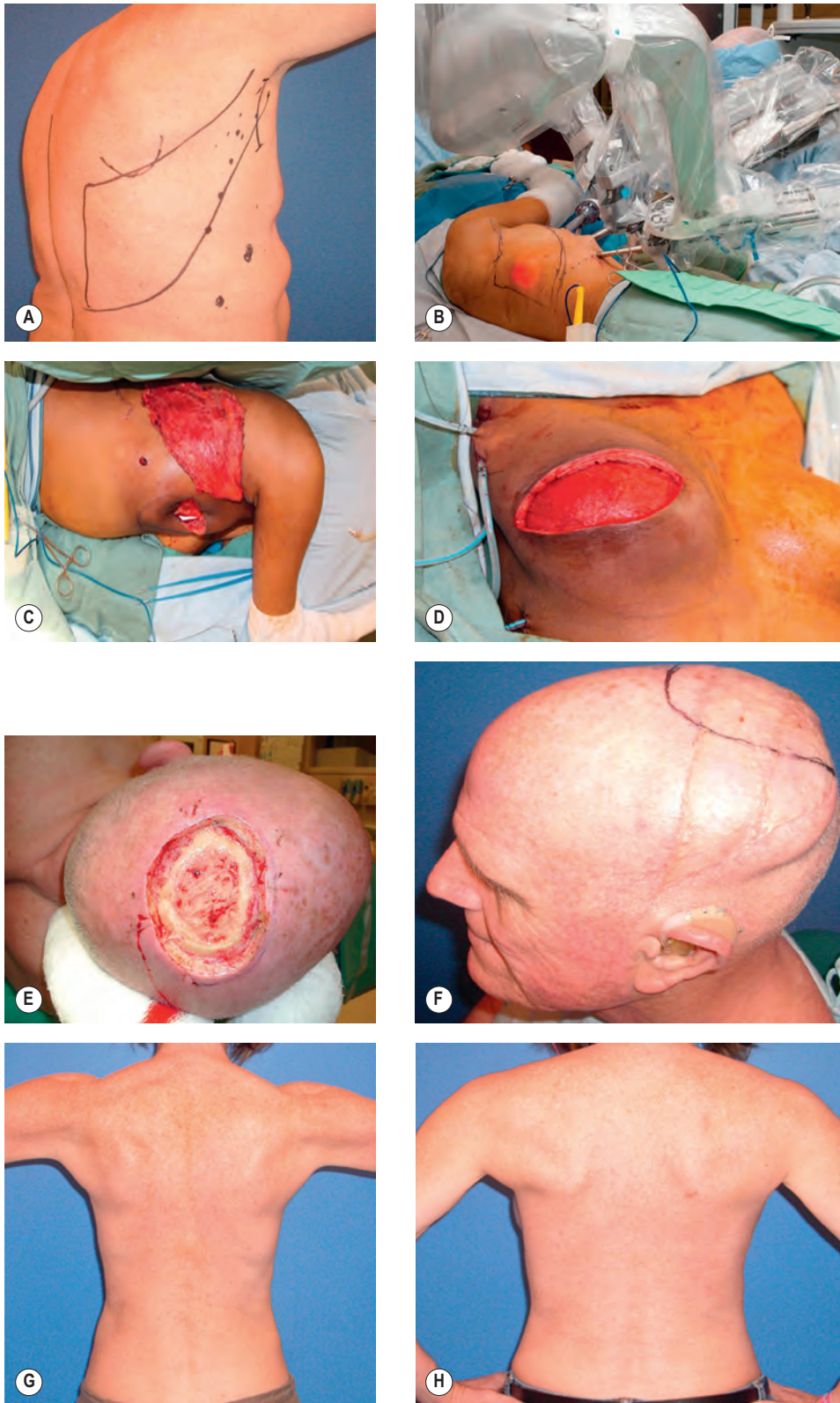


Fig. 34.4 (A) Markings and port placement. The borders of the latissimus dorsi muscle are marked according to anatomic landmarks. An axillary incision is then marked. For breast reconstruction, the sentinel lymph node incision is used. If a free flap is planned, then an incision is made that will facilitate pedicle dissection, dissection of the subcutaneous space anterior to the muscle, and placement of a port at the inferior end. Two additional ports are marked 8 cm from the end of the axillary incision and anterior to the muscle and 8 cm distal to the second port and anterior to the muscle. (B) After port placement, the robotic side cart is positioned posterior to the patient with the two robotic arms and the endoscope extending over the patient in proximity to the ports. (C) Transposition of latissimus dorsi muscle underneath a subcutaneous skin bridge. (D) Latissimus dorsi muscle achieves total muscle coverage over a permanent silicone shaped implant. (E) 90-cm² scalp defect from resection of a squamous cell carcinoma. (F) Three weeks postoperatively, his scalp is well healed, and he is marked for radiation simulation. (G–H) Case of immediate breast reconstruction following a right nipple–areola complex-sparing mastectomy. Besides a very minor contour defect, there is little appreciable difference in the appearance of the donor site before (G) and after (H) surgery. (A,B,E,F from Selber JC, Baumann DP, Holsinger FC. Robotic latissimus dorsi muscle harvest: a case series. *Plast Reconstr Surg.* 2012;129:1305–1312. C,D,G,H from Clemens MW, Kronowitz S, Selber JC. Robotic-assisted latissimus dorsi harvest in delayed-immediate breast reconstruction. *Semin Plast Surg.* 2014;28:20–25.)

Robotic training in plastic surgery

Another important question affecting broader application of robotic-assisted surgery is learning curve. When operating the robot, a comprehensive understanding of its mechanics,

kinetics, and operative dynamics is a major prerequisite; basic functionality alone is not enough. Therefore, a significant amount of time and energy should be spent on learning the subtle nuances of the robotic mechanics to be able to troubleshoot the machine when it is not performing optimally.



Fig. 34.5 (A) Markings and port placement. The contralateral costal margin and iliac crest are marked along a line connecting the anterior axillary line and the anterior superior iliac spine. The midpoint between these two landmarks and 2 cm lateral to it is the desired location of the 12-mm camera port. On either side of the camera port is the planned location of the two 8-mm instrument ports. (B) All three ports are in place and the robot is ready to be docked. (C) Docking the robot. The surgical robot is brought into position perpendicular to the patient on the ipsilateral side to the muscle being harvested. (D) The dual-console system. Instruments can be passed from one surgeon to the other for teaching purposes and the teacher can “telestrate” on the screen so the learner can be guided. (E) After having an exposed and infected arthroplasty endoprosthesis, this patient received a robotically harvested rectus muscle to cover the prosthesis. (F) The donor site. The scars are three small incisions on the contralateral side to the muscle being harvested. (G) After having an exposed medial ankle, this patient also received a robotically harvested rectus muscle flap. (H) The donor site is limited to the three ports because the muscle can be removed through one of the ports using a gallbladder bag. (A–F from Pedersen J, Song DH, Selber JC. *Robotic, intraperitoneal harvest of the rectus abdominis muscle. Plast Reconstr Surg.* 2014;134:1057–1063. G,H from Ibrahim AE, Sarhane KA, Pederson JC, Selber JC. *Robotic harvest of the rectus abdominis muscle: principles and clinical applications. Semin Plast Surg.* 2014;28:26–31.)

Appropriate teaching modules and evaluation and credentialing systems for specific plastic surgical skill sets do not yet exist despite much technological advancement. Surgical training curricula have stayed more or less the same for more than a century. Residents and fellows have always learned surgery through “supervised trial and error” on patients. This method makes training completely dependent on the case load; it may even prolong surgical training in some cases. Such an approach cannot be extended to robotics as current caseloads are very limited; this makes the learning curve for robotic surgery very

long. In this regard, simulation centers might be a better medium for acquisition of robotic surgical skills. In such settings, trainees can use surgical robots to practice operations on three-dimensional, virtual-reality visual simulations and soft-tissue models that recreate the textures of human tissues through force feedback (haptics).^{45,46} Furthermore, trainees can be supervised through tele-mentoring. This approach has the potential to considerably improve the learning curve of robotic surgery, allowing trainees to acquire robotic skills in a relatively shorter period while minimizing surgical errors and

thus enhancing patient safety. We must work as a specialty to define competency in robotic plastic surgery to insure it is being done safely and according to best practices.

For robotic microsurgery training, considering its technical complexity and the consequences of its failure, advanced teaching modules and robust learning assessment tools are needed to ensure a solid training and safe use. Unlike many other robotic versions of open procedures, robotic microsurgery combines the same principles as conventional microsurgery (for which a number of training modules already exist)^{47,48} with an additional skill set unique to the surgical robot. To better assess trainees and evaluate this mixture of skills, the senior author created the Structured Assessment of Robotic Microsurgery Skills. This evaluation system combines the Structured Assessment of Microsurgical Skills scoring system with other validated skill domains pertaining specifically to robotic surgery.⁴⁹ The Structured Assessment of Robotic Microsurgical Skills includes three parameters to assess conventional microsurgical skills, including: (1) dexterity, (2) visuospatial ability, and (3) operative flow. The robotic skills incorporate five additional parameters, including: (1) camera movement, (2) depth perception, (3) wrist articulation, (4) atraumatic tissue handling, and (5) atraumatic needle handling. Each parameter is scored from 1 to 5, with 1 being the worst and 5 the best. The overall performance and overall skill level are also assessed independently.^{50,51} We have recently used this new robotic microsurgical evaluation system to plot the maturation process of these skills in a heterogeneous cohort of surgeons including clinical fellows, research fellows, and experienced microsurgeons. In this study, we successfully validated this new assessment instrument with excellent consistency and high levels of interrater reliability. We were further able to demonstrate improvement in robotic microsurgical skill across our heterogeneous group of learners. All skill areas and overall performance improved significantly for each participant over the five robotic microsurgery sessions. Operative time decreased over the study for all participants. The results showed an initial steep technical skill acquisition followed by more gradual improvement, and a steady decrease in operative times that ranged between 1.2 hours and 9 minutes. We found that prior experience with conventional microsurgery did in certain areas improve the acquisition of technical proficiency using the robotic system. All groups demonstrated an ability to gain proficiency in robotic microsurgical anastomosis with minimal robot-specific training, indicating that the technical aspects of robotic microsurgery can be gained by learners with no prior microsurgery or robotic experience.⁵² In our prior study of conventional microsurgical assessment data using the Structured Assessment of Microsurgical Skills,⁵³ moderately experienced subjects improved in skill through the middle and upper range of scores.^{53–55} By contrast, in the current study, subjects with no prior experience in robotic microsurgery moved through all but the highest level of Structured Assessment of Robotic Microsurgical Skills scores to achieve proficiency.^{54–57} Because of the inherent benefit of the robotic surgical platform for microsurgery, there is considerable interest in defining its role. To do this in an organized, controlled, and systematic fashion, we have developed a well-defined anastomotic model, a validated assessment tool, and a general sense of the trajectory of learning. These steps are the first on the road to customized education, curricular design with

individual assessment, targeted feedback, and competency-based learning.

New frontiers in robotic plastic surgery

The specific disadvantages of the robotic platform include: (1) lack of haptic feedback, (2) inferior optics as compared to the operating microscope and (3) instrumentation which is poorly adapted to microsurgery. All of these, however, are platform-specific (and not inherent to the field), and thus can be potentially overcome with incrementally improved technology.

A new “six degrees of freedom” test platform, the μ Haptic device, with microsurgical tele-robotics and simulation, was designed and built by a research group in Stanford (although still not formally tested in an animal model to date).⁵⁸ In addition, a new robotic platform that is expected to be available soon (ALF-X multi-port robotic system) will be equipped with platform-exclusive features, such as haptic feedback, possibly enabling endoscopic super-microsurgery.⁵⁹

As for the optics, the telescope-based high-definition video system (VITOM, Karl Storz, Tuttlingen, Germany) which offers 16–18 $\times$ optical magnification (comparable to the operating microscope) has been recently integrated into the robotic TilePro system (Intuitive Surgical Inc.) to provide the microsurgeon with a cockpit view of all video inputs; it can be positioned on an additional fifth robotic (nitrogen-powered, Karl Storz) arm (Fig. 34.6). It has been used so far for robot-assisted vasovasostomy (RAVV) and vasoepididymostomy (RAVE), with improvement in operative time and comparable results to those of traditional microscopic reversal.⁶⁰ Parekattil's group is also involved in clinical trials of a 100 $\times$ digital camera (Digital Inc, China) that can be utilized via the TilePro daVinci S or Si robotic system (Intuitive Surgical, Sunnyvale, CA) to allow the surgeon to toggle or use simultaneous 100 $\times$ and 10–15 $\times$ visualization.²⁹ This has the

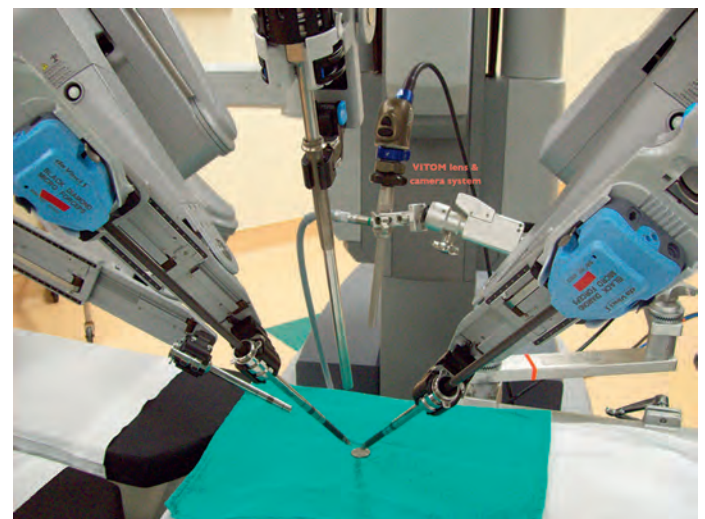


Fig. 34.6 Operative set-up for the robotic platform with the additional VITOM lens camera system and point setter nitrogen-powered arm (fifth arm, center of image). (From Parekattil SJ, Gudeloglu A, Brahmabhatt J, et al. Robotic assisted versus pure microsurgical vasectomy reversal: technique and prospective database control trial. *J Reconstr Microsurg.* 2012;28:435–444.)

potential for an unparalleled visual acuity for complex microsurgical procedures.

Other microsurgery-specific robotic instrumentation, of potential interest to reconstructive microsurgeons, include the flexible drop-in Doppler (Vascular Technology Inc., Nashua, NH) designed specifically for use with the robotic platform. It is easily manipulated by the robotic forceps, and allows the surgeon to perform real-time Doppler monitoring of the surrounding vasculature and tissue. Also, a robotically controlled ultrasound transducer (Aloka Inc., Wallingford, CT) has recently been developed and allows surgeons to obtain full ultrasound imaging with real-time flow mapping.⁶¹ Another potentially useful modality is hydro-jet dissection, utilizing a thin, high-pressure stream of water for fine tissue dissection while preserving vascular integrity; this technology can be applied robotically with a pressure-adjustable device such as the ERBEJET2 hydrodissector (ERBE Inc., Tübingen, Germany).^{62,63} Finally, CO₂ laser dissection, which is currently growing in popularity as it can provide effective ligation and coagulation with less collateral thermal damage,⁶⁴ has been integrated into a flexible fiber-optic delivery system manipulated with a robotic handpiece attached to a robotic arm (FlexGuide ULTRA and BeamPath Robotic Fiber, OmniGuide, Cambridge, MA). The fiber-optic CO₂ laser might even substitute monopolar or bipolar cautery for microsurgical dissection, where maintaining the integrity of the surrounding

structures is crucial. As the use of robotic microsurgery expands, so will the refinement and development of new and adapted instrumentation.

Conclusion

Minimally invasive techniques have long been known to reduce postoperative pain, hospitalization duration, patient recovery time, infection risks, and overall cost, increasing the quality of care.⁶⁵ Robotic technology is the next step in the evolution of minimally invasive techniques, adding enhanced precision and visualization that can augment the capabilities of plastic surgeons and aid them in achieving safer and more precise interventions. Additionally, these technologies can enable surgeons to perform approaches never before possible, such as the robotic LD harvest. Robotic instrumentation is also expected to continue to improve and expand the range of applications in various areas within plastic surgery, especially microsurgery, leading potentially to the refinement of procedures and wider adoption. The future of robotics in plastic surgery is promising. With improved technology platforms, improved training pathways and the inevitable decreases in cost which accompany the democratization of all technology revolutions, robotic plastic surgery will likely grow and flourish.



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Telemedicine and simulation in plastic surgery

Joseph M. Rosen and M. Lucy Sudekum

SYNOPSIS

- This chapter describes the latest innovations in simulation and telemedicine and their integration into plastic surgery practice.
- Simulation will have its greatest impact on the teaching and performance of plastic surgery. Simulation is used to train plastic surgery students, residents and fellows in all procedures, and to train senior surgeons on new procedures. Simulation provides an increase in safety and reduction in medical errors, since trainees will effectively “make mistakes” on a simulator, rather than on live patients.
- Telemedicine will have its greatest impact on plastic surgery delivery. Telemedicine can make use of simulation and new technology to deliver medical care to a distant population, whether during everyday life, in wartime, or following a disaster.
- This chapter will provide plastic surgeons with a basic understanding of how to apply current technologies to enhance their armamentarium with solutions to clinical and surgical problems.

Introduction

Medical technology can help doctors to diagnose, heal, and transcend traditional limitations of the human body, via tools like pacemakers, ventilators, artificial hips, three-dimensional (3D) body imaging, and even robotic arms. Plastic surgery, a specialty that prides itself on approaching complex problems with innovative solutions, has an opportunity to lead the medical community in the responsible and creative use of new technology.

Surgeons can enhance their practice with biological technologies, such as transplantation and tissue engineering, covered in Chapters 12, 16, 30, 32, 33, or with nonbiological technologies. This chapter discusses the latest innovations in nonbiological technologies – simulation and telemedicine – and their widespread integration into plastic surgery practice. Simulation is used to train plastic surgery residents in common procedures, and to train senior surgeons on new procedures. Simulation promotes safety, as trainees will make initial errors on a simulator before operating on live patients. Finally, access

to mobile sophisticated technology via smartphones has placed telemedicine in the hands of a larger population than has been previously imagined.¹ This aspect of telemedicine delivers medical care to a distant population, whether during everyday life, in wartime, or following a disaster.

This chapter will provide plastic surgeons with a basic understanding of how to apply current technologies to enhance their armamentarium with solutions to clinical and surgical problems. Technological tools can resolve needs that are not met with current standards of care (for example, a potentially concussed football player can consult with a neurologist via telemedicine without leaving the playing field).² However, it is critical that both outcomes and costs be considered whenever we evaluate new technology; the outcomes should be demonstrable, and the cost-benefit ratio considerable.

Simulation



Access the Historical Perspective section and Fig. 35.1 online at

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Introduction and definition of simulation

Simulation is increasingly utilized in surgery as the field reacts to continued pressure to standardize training. The main push for standardization comes from the desire to improve patient safety. Simulation can be defined as “the imitative representation of the functioning of one system or process by means of the functioning of another.”⁹ This includes the use of a model, whether physical or logical, over time, to gain insight into the way the system or process operates in order to evaluate and analyze it.⁷ This chapter’s focus is on computer-based simulators that engage the learner and test cognitive knowledge. Animation is a new feature that accompanies some computer-based simulators. Trainees first watch animated computer films, to view the specific procedure and

Historical perspective

Simulation has been used for centuries in various arenas. One early example includes military simulation in the sixth century in the form of the chess game.³ Widespread use of simulation across the aviation field draws the highest correlation with the field of medicine. Link created the first flight simulator in 1929 with the goal to develop a safer, less expensive, easier method to learn to fly.⁴ The US military served as the early investor of Link trainers in World War II, and later spurred the propagation of more complex simulators for flight training upon the advent of computer imaging.⁴ Later the National Aeronautics and Space Administration (NASA) invented modern virtual reality. These tools became ingrained in training regimens for both pilots and other members of the flight crew, and also

served as a method for personnel evaluation. Contemporarily, flight simulators have proven to be not merely safe, but cost-effective, with cost ratio estimates of 1:40 for training with a simulator versus training in an aircraft.⁵

The earliest record of surgical simulators from 600 BC in India includes clay and leaf models for forehead-flap nasal reconstructions (Fig. 35.1).⁶ Other early examples of simulation in plastic surgery include Le Fort's use of cadavers to study facial fractures, and Rad Tanzer's use of plaster ears prior to completing reconstructive surgery on patients.⁷ Today medical device companies and technology are merging to create new horizons for simulating surgery and its modeling – for example, plastic surgeons can 3D-print patient models for precise surgical planning.⁸

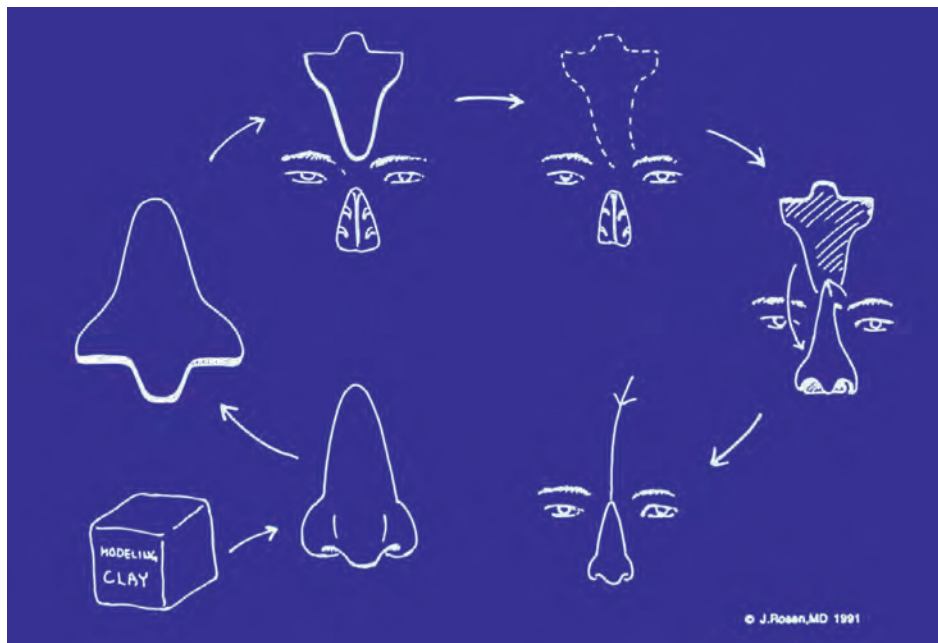


Fig. 35.1 Early surgical planning using modeling clay for nose flap. (Courtesy of Joseph Rosen, MD.)

become familiar with the relevant anatomy, before they practice the procedure on the computer-based simulator. This is analogous to the “see one, do one” approach for traditional surgical training.

Simulation can be implemented in three phases, based on the American College of Surgeons (ACS) plan for general surgery trainees: (1) it can be used to learn skills; (2) to practice and understand procedures; and (3) to practice team training in the operating room.⁷ Simulators, physical devices which manifest simulation in the medical area, can take various forms, including bench models, animal models, cadavers, mannequins and computer and online simulators.⁷ Specialized surgical skill workshops have reduced the rate of complications in endoscopic carpal tunnel procedures.¹⁰ Thus, when applied to medical procedures, ethically and practically, simulation provides an effective tool for both education and planning in a variety of surgical specialties. In plastic surgery, simulation has applications in residency training, maintenance of certification, and patient-specific planning of procedures. Simulation provides a safe and consistent way for plastic surgeons to improve and verify technical skills, cognitive knowledge, and teamwork.

Rationale for using simulation for plastic surgery and evidence of its utility in surgical training paradigms

Both the Accreditation Council for Graduate Medical Education and American Board of Medical Specialties sanction the common six core competencies for all surgeons: (1) medical knowledge; (2) patient care; (3) interpersonal and communication skills; (4) professionalism; (5) practice-based learning and improvement; and (6) systems-based practice.¹¹ Despite these aims, the Institute of Medicine reported that roughly 210 000–400 000 deaths in the US occur each year as a result of medical errors – significant enough to deem it a public health risk.¹² These staggering statistics have prompted greater concern for patient safety across the field. Furthermore, the rising cost of healthcare has put pressure on medical centers to alleviate costs. While operating room time has real costs up to thousands of dollars per hour,¹³ simulation provides a safe way for surgeons to practice procedures at a significantly reduced cost.⁷

Using virtual reality and simulation, residents and attending surgeons can practice skills and procedures without risk to the patient; it is a supplement to the “see one, do one, teach one” paradigm. If a trainee can practice certain skills and procedures on a simulator, operating room times can be reduced, and potentially fewer mistakes made by trainees, thereby increasing patient safety.

The role of simulation in plastic surgery

Training simulators

Simulation for training is growing in pervasiveness in plastic surgery, with early use in residency programs. While the ACS has pioneered the foundational structure for using simulators for training through its Accredited Educational Institutes (AEIs) consortium, the plastic surgery community has primarily focused on developing procedural simulators specific to the field. Technical skills are usually taught in general

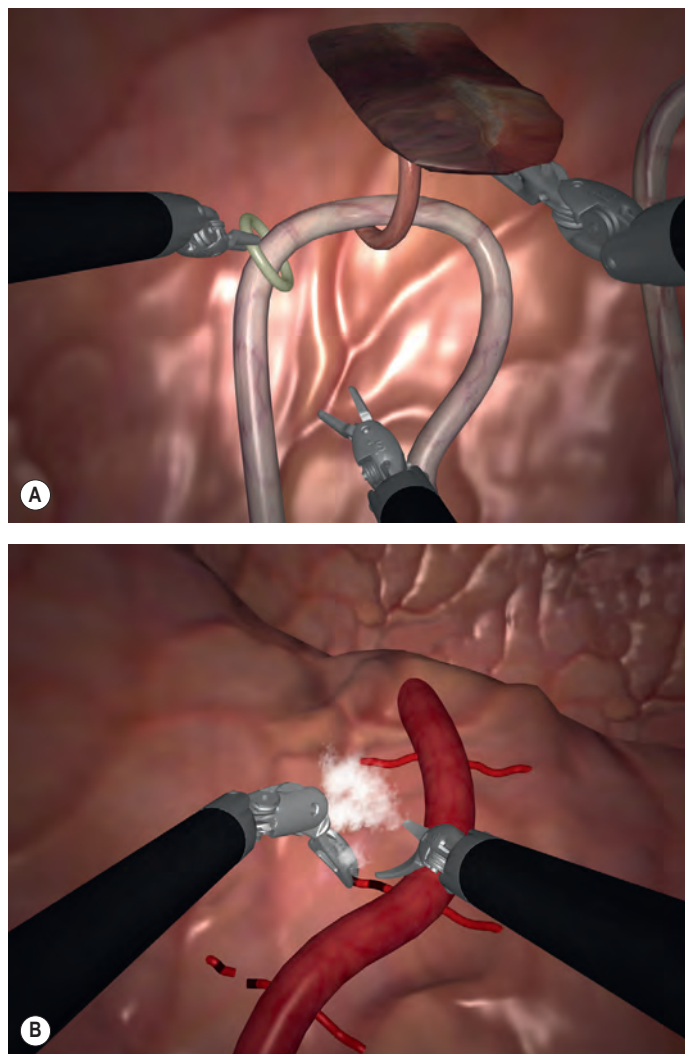


Fig. 35.2 The Mimic dV-Trainer simulator for robotic surgery is designed to train surgeons in how to use the da Vinci surgical system and to teach system awareness, instrument manipulation, and basic skills such as needle handling and energy management. **(A)** The Ring Walk exercise assists in refining dexterity, moving an object with a linear constraint, using the camera to navigate around the surgical field, and learning how to use the clutch with the instruments. **(B)** The Energy Dissection exercise instructs the user in applying the use of cautery and coagulation as part of dissection, as well as controlling blood loss. (Courtesy of Jeff Berkley, PhD, and Gordon Nealey; copyright 2012 Mimic Technologies, Inc.)

surgery training; the AEIs aid this process with skills simulators such as box trainers for suturing.¹⁴

As minimally invasive robotic surgery gains traction, simulators are likewise utilized to train on specific operating tools, such as the da Vinci system. The Mimic Technologies dV-Trainer, a simulator for the da Vinci system, is a tabletop virtual environment with a two-handed haptic device with force feedback and tracking (Fig. 35.2). A study by Kenney *et al.* revealed that the dV-Trainer had content, construct, and face validity, which is a positive assessment of the simulator’s realism by the novice user.¹⁵ Intuitive Surgical also offers the da Vinci Skills Simulator, introduced in 2011. Designed to offer an immersive virtual experience via the surgeon console, the da Vinci simulator enables users to measure and track skills assessment without the need for additional system components, instruments, or skills models. The use of

simulators for robotic surgery training is explained in more detail in Chapter 34.

The American Council of Academic Plastic Surgeons (ACAPS) *Ad Hoc* Committee on Virtual Reality and Simulation for Plastic Surgery Education is committed to helping develop and distribute simulators to educate residents on plastic surgery procedures. The Committee is divided into groups of experts in four plastic surgery subspecialties: (1) craniofacial; (2) cosmetic; (3) reconstructive; and (4) hand procedures. A survey completed by 85 ACAPS members in February 2009 indicated that 93% were interested in using a 3D surgical simulator system for training residents in plastic surgery. Today this is a reality.

The Committee's goals are to adapt this advanced virtual surgery simulation technology for standardized teaching, and for procedures in the four aforementioned areas of expertise. Using a process called cognitive task analysis, procedures such as open carpal tunnel release and reduction mammoplasty are broken into steps, which are weighted according to their relevance to the outcome of the procedure. For instance, in the latissimus dorsi procedure, flap positioning and chest closure are weighted at 20%, while dressing is 5%. In this way, key teaching points are emphasized in the developed simulator.

BioDigital Inc. and the NYU Institute of Reconstructive Plastic Surgery have undertaken the development of animators and simulators to educate residents in plastic surgery procedures. Using a multidisciplinary team of plastic surgeons as medical experts, artists to provide realism, and computer scientists for technical development, the team has created a library of training programs to teach craniofacial and breast procedures. Table 35.1 summarizes the procedures for which animations have already been completed.

The SmileTrain and BioDigital cleft lip and palate simulator, developed under the leadership of Dr. Roberto Flores, MD, is an online platform allowing the user to explore the procedures in depth online (Fig. 35.3). Its CT-based patient model enables the trainee to practice, record, and review surgery in real time; to explore the anatomy at every tissue layer; and to cut surfaces, create flaps, and transpose tissue.^{16,17} Simulators in the *Interactive Craniofacial Surgical Atlas*, created under the direction of Joseph McCarthy, MD, include the frontal orbital advancement simulator, the Monoblock advancement/distraction simulator, and the Le Fort III

Table 35.1 Completed surgical animations for various surgical procedures

Problem	Animated procedure
Bilateral cleft lip	Cutting bilateral procedure
Secondary cleft lip nose	Dibbell procedure
Unilateral cleft lip	Mohler procedure
Cleft palate	Furlow (primary palate)
Genioplasty	Sliding genioplasty Jumping genioplasty
Prognathia	Bilateral sagittal split osteotomy Vertical ramus osteotomy
Temporomandibular joint ankylosis	Transport distraction
Maxillary hypoplasia	Le Fort I
Midface deformities	Le Fort III classic and distraction
Upper two-thirds hypoplasia	Monobloc distraction Monobloc classic
Craniosynostosis	Fronto-orbital advancement
Breast reconstruction	Pedicle TRAM reconstruction DIEP flap reconstruction Latissimus dorsi flap reconstruction Free TRAM reconstruction Tissue expander
DIEP, deep inferior epigastric perforator; TRAM, transverse rectus abdominis myocutaneous.	

advancement/distraction simulator. These new simulators include features such as videos of live surgeries, to help illustrate the procedure being simulated; audio voiceover, to facilitate learning as the trainee practices; and 3D visualization (Fig. 35.4). Simulators for other specialized procedures include a simulator for latissimus dorsi myocutaneous flap with tissue expander for breast reconstruction following mastectomy (Fig. 35.5).

For example, the University of Wisconsin has developed an Endoscopic Carpal Tunnel Release (ECTR) simulator that is being used by resident subjects (Fig. 35.6). The subjects are asked to take a pre-preparation test followed by randomization into simulation and non-simulation groups for

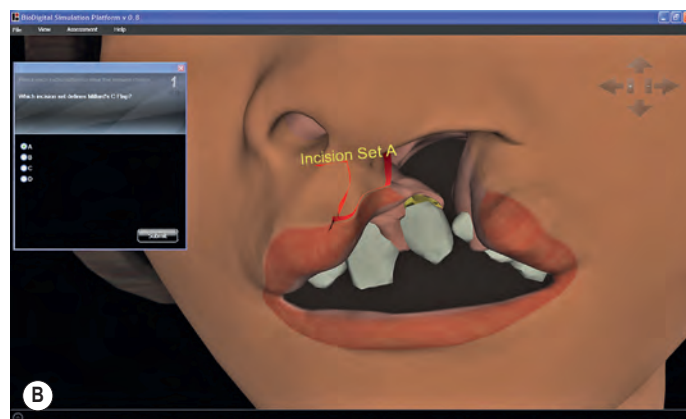


Fig. 35.3 BioDigital Inc./SmileTrain cleft lip and palate simulator showing a simulated patient's appearance (A) before and (B) during surgery. (Courtesy of SmileTrain and BioDigital Inc. Available online at: <https://smiletrain.biodigital.com/#/>.)

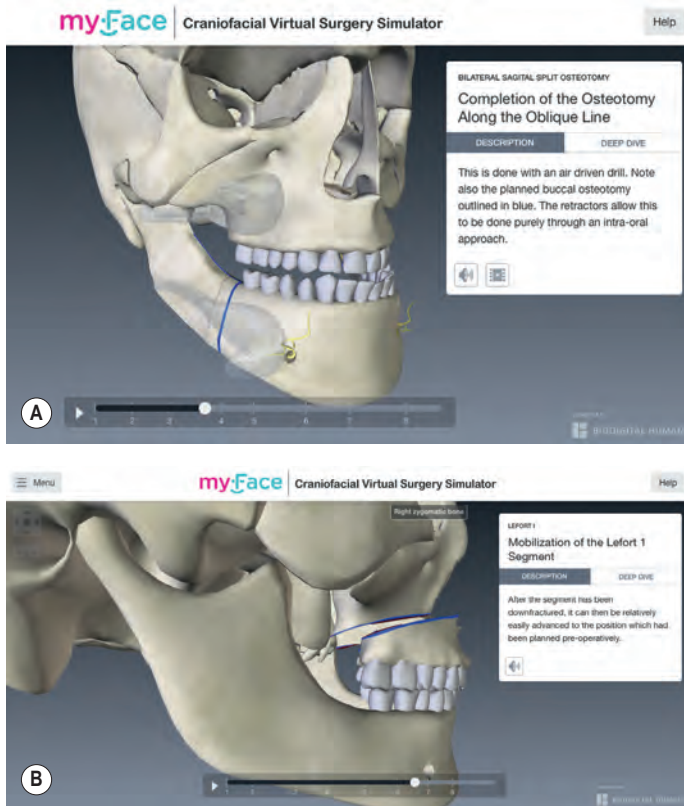


Fig. 35.4 MyFace craniofacial virtual surgery simulator (A) bilateral sagittal split osteotomy procedure and (B) LeFort I procedure. (Courtesy of MyFace, Joseph G. McCarthy, MD, and BioDigital Inc. Available online at: <https://civapro.biodigital.com/#/>.)

comparison. The simulation group uses the simulator, which focuses on surgical indications, relevant anatomy, and procedural steps, followed by a physical model simulation and a post-preparation test. The non-simulation group prepares for the case as they would for any other surgical operation. All subjects undergo a real-time ECTR case with the senior author and are assessed on a 20-point objective scoring measure: operating set-up, anesthesia, tourniquet, procedure steps, dressing application, etc. The subjects had different surgical backgrounds but overall it was found that the simulator group outperformed the non-simulation group on post-preparation test scores (89% vs 74%; $p < 0.001$) and operative scores (96% vs 79%; $p = 0.002$). The subjects showed significant improvement in all steps of the operation except for dressing application. This study and those like it show the promise and future of surgical training and its benefits (B. Mandel, personal communication).

Arguably the most advanced simulation system available to surgical trainees is the Wide Area Virtual Environment (WAVE) that was developed by Alan Liu at the Val G. Hemming Medical Simulation Center of the Uniformed Services University of the Health Sciences (A. Liu, personal communication). The WAVE is a 1000 sq ft immersive virtual-reality training environment that combines 3D virtual environments with patient actors, human patient simulators, and the theatrical effects to provide comprehensive and unprecedented levels of realism (Fig. 35.7). As seen in Fig. 35.7A, projectors are placed around the training operating theater and triage area allowing for constantly changing scenarios.

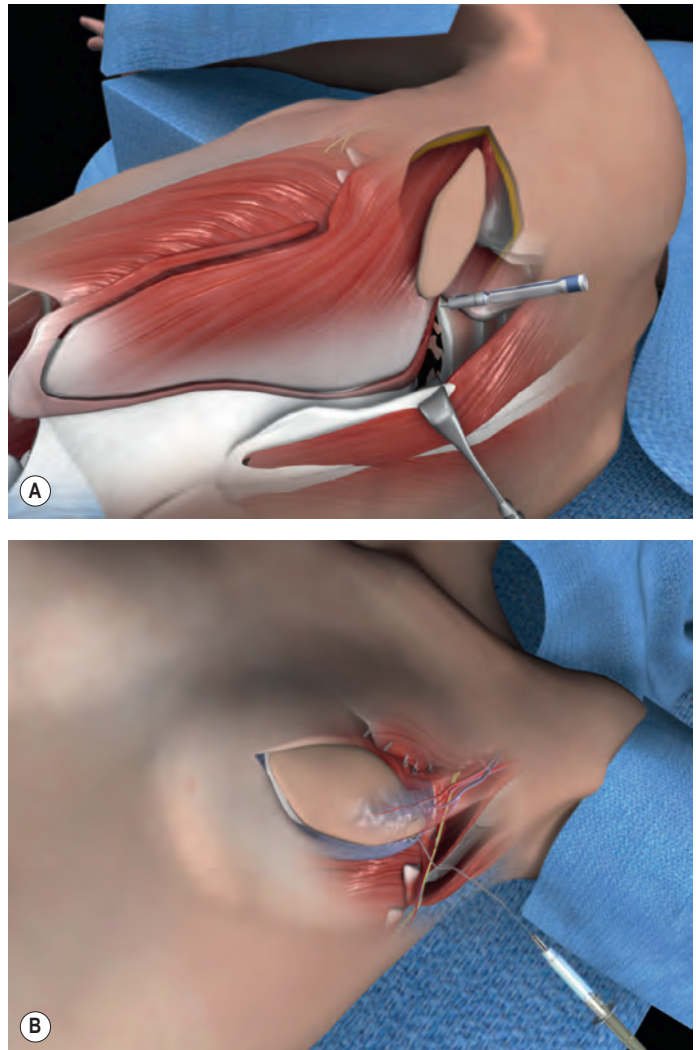


Fig. 35.5 BioDigital Inc. latissimus dorsi simulator. (Courtesy of BioDigital Inc.)

The WAVE is designed to support training scenarios of up to 96 hours in duration.¹⁸

Investigators at Dartmouth's Thayer School of Engineering have conducted team-training research to enhance communication and ensure safe patient handoffs between operating room personnel and hospital staff. The envisioned system – a computational team-training simulation – will seamlessly monitor medical operations to reduce or prevent catastrophic medical errors and to improve patient safety (E. Santos, personal communication). The Santos team models reasoning among doctors, nurses, and patients,¹⁹ and simulates the team's clinical decision-making and reasoning prior to, during, and after surgical procedures, to analyze inconsistencies or gaps in the procedure – a key indicator of medical errors – with the goal of alerting the team when any discrepancy occurs.

Surgical planning simulators

Plastic surgeons can use simulation not only to practice new procedures on a virtual patient, but also for patient-specific surgical planning. Prior to the first US near-total face transplant procedure, performed by a surgical team led by Dr. Maria Siemionow at Cleveland Clinic in 2008, the surgeons used anatomical models made from the patient's CT scans,

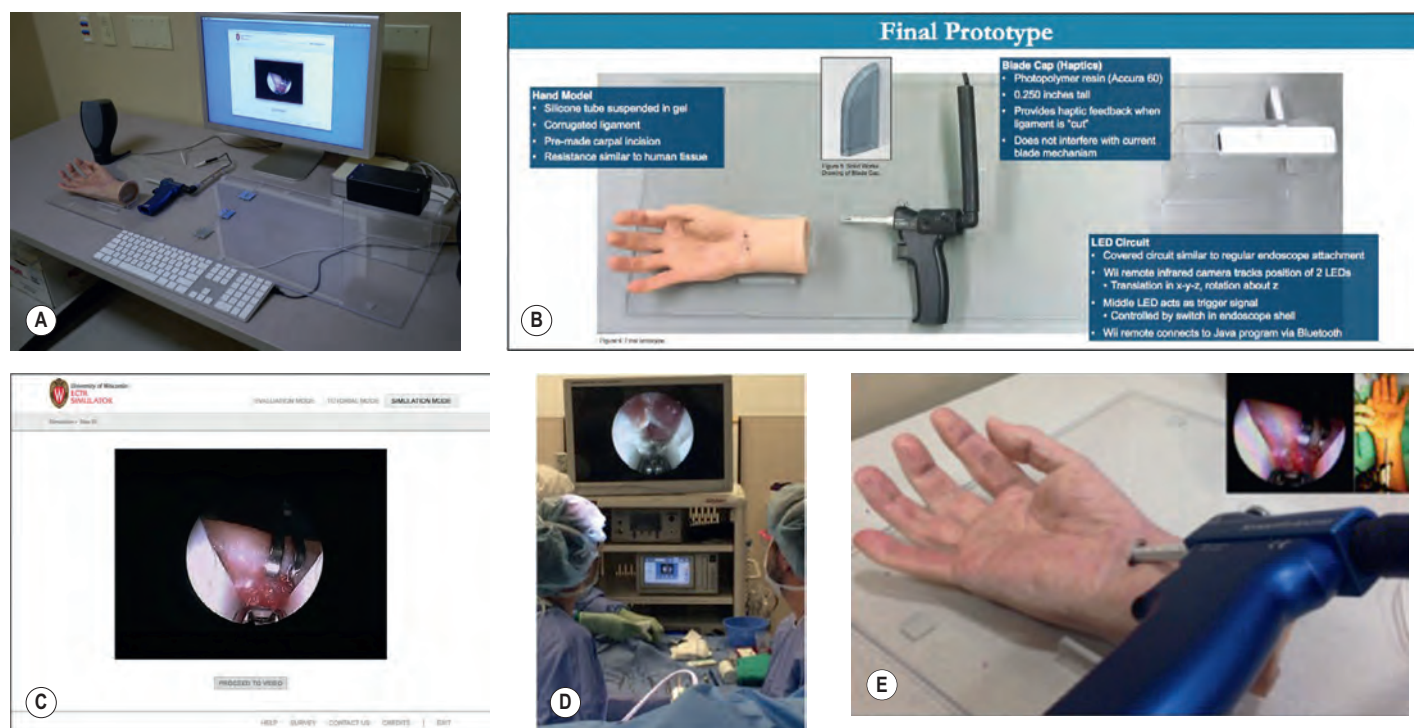


Fig. 35.6 Endoscopic Carpal Tunnel Release (ECTR) simulator. (A) Simulator set-up. (B) Detailed simulator set-up. (C) Simulator in use. (D) Comparative OR set-up. (E) Simulator in use with simulator screen and OR comparison. (Courtesy of Benjamin Mandel, MD; Steve Kempton, MD; Jacqueline Israel, MD; A. Neil Salyapongse, MD.)

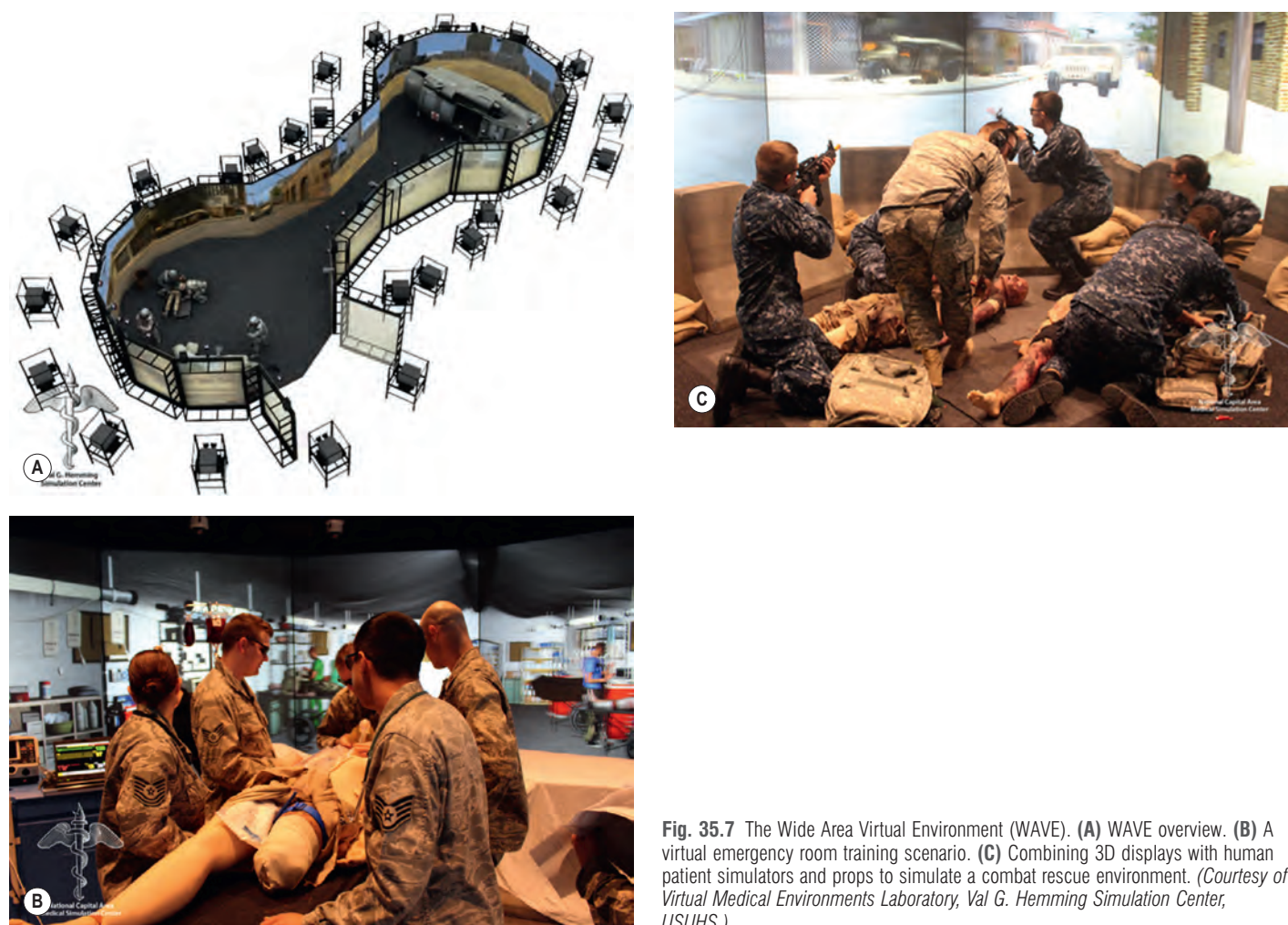


Fig. 35.7 The Wide Area Virtual Environment (WAVE). (A) WAVE overview. (B) A virtual emergency room training scenario. (C) Combining 3D displays with human patient simulators and props to simulate a combat rescue environment. (Courtesy of Virtual Medical Environments Laboratory, Val G. Hemming Simulation Center, USUHS.)

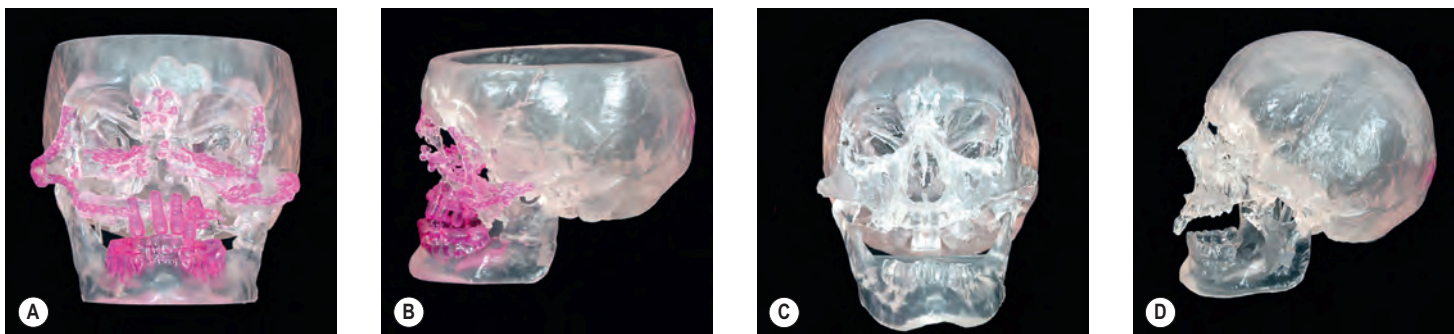


Fig. 35.8 The stereolithographic anatomical model based on the computed tomographic scan of the patient who had the first US facial transplant, performed by a team of surgeons led by Dr. Maria Siemionow at the Cleveland Clinic in 2008. **(A)** Frontal view of the craniofacial defect after gunshot injury to the patient's face, indicating damage of the frontal and midface skeleton including the infraorbital floor and the nasal, zygomatic, and maxillary bones mixed with the metal pieces. **(B)** The left side of the defect, with a significant tridimensional defect showing missing nose and nasal bones and upper jaw bony support. **(C)** Frontal view at 6 months after transplantation, demonstrating complete restoration of the craniofacial defect by replacement of all missing bony components of the facial skeleton and soft tissues of the patient with the composite facial allograft from the donor. **(D)** Left-side view after transplantation confirming restoration of the tridimensional defect of the craniofacial skeleton, including nose and bony structures supporting the upper and midface skeleton. (Reproduced with permission from Siemionow MZ, Papay F, Djohan R, et al. *First U.S. near-total human face transplantation: a paradigm shift for massive complex injuries*. *Plast Reconstr Surg*. 2010;125:111–122.)

showing the facial defect, as part of their surgical planning (Fig. 35.8)²⁰ (M. Siemionow, personal communication).

Prior to the second US facial transplant, performed by microsurgeons at Brigham and Women's Hospital in 2009 under the leadership of Dr. Bohdan Pomahac, the team also used CT scans of the recipient's head and facial defect to generate a life-sized 3D model of the cranium, built in acrylic. The team then generated a second 3D facial model, based on a CT scan of normal facial anatomy, from which parts were removed and transferred to the recipient's model. This allowed the surgeons to plan how much bone was needed from the donor, as well as to anticipate the anatomical logistics of the donor recovery procedure (B. Pomahac, personal communication).

Future applications of simulation

A future vision must include simulation trainers in plastic surgery plans universally, and also provide training for new procedures as part of continuing education, in a safe, efficient, and effective manner. As simulation centers are developed in increasing numbers, and medical center and surgery curricula continue to incorporate simulation as a beneficial tool for training, simulation will become more ingrained in the field of plastic surgery for resident training, maintenance of certification, and patient-specific practice. As simulators become more advanced, they will be used at various levels in practice, and may even incorporate a physical-behavioral-genomics model of a human being, one that combines information about a person's cells, tissues, organs, vital signs, biomechanics, physiology, behavior and genetic traits, combined with the epidemiology of a larger population. Such a comprehensive model might simulate and predict the individual's behavior and health (Fig. 35.9).

Telemedicine



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Introduction

In the future, telemedicine will extend robotics and simulation to make plastic surgery safer, simpler, more successful, and more accessible. The patient-provider relationship and delivery of care will be transformed by telemedicine, as doctors will not need to be physically present in order to care for their patients. This section of the chapter defines telemedicine as a clinical tool, explains the role of social networks in telemedicine, presents potential challenges in its utilization for plastic surgery, and explains current and future applications in plastic surgery.

Definition and methods

Telemedicine refers to the application of telecommunications technologies to a medical context. Telemedicine may be defined as "a branch of e-health that uses communication networks for delivery of healthcare services and medical education from one geographical location to another".³¹ Telemedicine may be as simple as faxing a copy of an X-ray, or as complicated as multipoint video conferencing across several continents with high-resolution image transfer. A resident can ask an attending physician for advice; one physician can ask another physician for advice; or a patient can ask advice of a doctor. Many components of current plastic surgery consultation can be converted to a digital format, including long-distance triage, remote consultation, telesurgery,^{32,33} postoperative assessments, patient education, continuing medical education for providers, and public health education.

Worldwide, the need for telemedicine has only increased as the gap in access to technology broadens between those living in rural and urban areas. People living in rural areas have less access to medical care generally, and in many cases, to specialty care, with the exception of medical volunteerism groups such as ReSurge International (formerly Interplast).³⁴ ReSurge International is one of a number of groups that provide temporary specialty care to remote areas on international surgical humanitarian trips, and supplement this with visiting educators who provide direct, hands-on training for local medical personnel. The interaction with local

Historical perspective

NASA helped pioneer telemedicine in the 1960s: when humans began flying in space, physiologic parameters were communicated between both the spacecraft and the space suits during missions.²¹ Fifteen telemedicine projects were active by 1975, with pioneering efforts in the US and worldwide. The earliest-reported nongovernment applications of telemedicine included a teleradiology effort at the Montreal Neurological Institute and a telepsychiatry network at the Nebraska Psychiatric Institute.²¹ Early projects using telemedicine in rural healthcare proved to have great beneficial effects on survival and recovery of patients; as the cost and size of the equipment came down and the technical quality went up, telemedicine became feasible to use in different applications, including maritime medicine and care in remote locations, including Antarctica.^{22–26}

Telemedicine has followed the enormous growth of computing and the internet from 1980 to the present day. Whereas

in 1980 almost no one had a home computer or cell phone, and the internet was in its infancy, now most people in developed countries have home computers, internet access, and mobile phones, making it possible for people to work remotely and telecommute; do online banking, travel reservations, and web shopping; and use email and social networks. A similar transformation occurred in medicine: it is now possible to link from home or a small clinic or medical center using video conferencing and other telemedicine technologies to access specialists worldwide for consultation and even surgery.^{27–29} Telemedicine is increasingly benefiting from the technology that allows us to collect and transmit medical information using portable devices such as ultrasound monitors and cell phones. For example, Remote Interaction, Consultation, and Epidemiology (R.I.C.E.) uses SMS technology to track influenza and diarrheal diseases in rural Vietnam.³⁰ Networked medical care has a great potential to improve both daily patient care and also to allow clinicians to respond to various medical disasters anywhere in the world at any time.

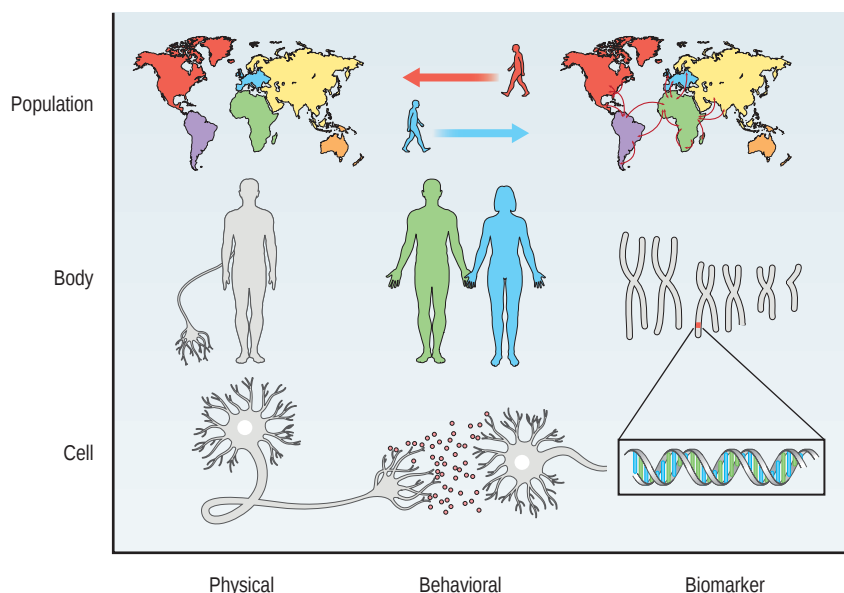


Fig. 35.9 Physical-behavioral-genomics model. No model yet exists that encompasses the physical body, behavior, and biomarkers of an individual, but Dr. Joseph Rosen and colleagues are developing such a model. A full human model could include a person's cells, tissues, organs, vital signs, biomechanics, physiology, behavior and genetic traits, combined with the epidemiology of a larger population. Such a comprehensive model might simulate and predict the individual's behavior and health. (Courtesy of Joseph Rosen, MD.)

providers is such that surgeons in host countries can post cases on a secure website to receive advice when ReSurge International teams are not in-country. Specialist physicians, such as plastic surgeons, are often a small percentage of the overall physician workforce and tend to be concentrated in urban centers. Through this networked-care mechanism, we are moving toward more efficient use of specialists as their time and expertise are available anywhere, anytime.³⁴

Several technologies are commonly used in telemedicine applications. The first, called store-and-forward, is used to transfer digital images from one location to another. An image is taken with a digital camera (store) and then sent (forward) to another location for interpretation and analysis (Fig. 35.10). This method is used for nonemergent situations, when a consultation can be provided in the next day or few days, and a patient's wellbeing is not dependent on an immediate response from a physician.

Another technology often used in telemedicine applications is called the synchronous model. This technology is used when a face-to-face interaction is desired, and is used between a patient/provider in one location and a specialist in another location. It provides real-time relay of information and can allow for review of information by on- and off-site personnel (Fig. 35.11).³⁵ In most cases, the patient/provider pair is located in a rural environment and the specialist is located in an urban center. These types of patient consults are becoming commonplace in medical practice. Dartmouth-Hitchcock Medical Center's Division of Plastic Surgery is developing a follow-up telemedicine program. Programs like this one are only being used when a physician-patient relationship has already been established. (See below for telemedicine regulations and legal constraints.) Once the relationship has been established, the patient can be screened and enrolled in these programs to avoid follow-up appointments at the hospital. These telemedicine visits can take the place of face-to-face clinical visits. This is both cost- and time-efficient for the patients (Figs. 35.12 & 35.13). Video conferencing equipment at both locations enables a live, real-time consultation for the patient without having to travel (Table 35.2).

Social networking

The future delivery of healthcare will not be limited to face-to-face interactions. Online social networks, such as [Patients-LikeMe.com](#) and [CarePlace.com](#), already link patients with similar conditions. Clayton Christensen, in *The Innovator's Prescription*, discusses facilitated networks as an important part of a future healthcare system.³⁶ The websites previously mentioned already exist for patients as facilitated networks. In the plastic surgery realm, [www.obesityhelp.com](#) is a website where patients can find resources on weight loss surgery, including a body mass index calculator, research, forums, insurance assistance, pictures, providers, and stories.³⁷ Facilitated networks can exist specifically for plastic surgeons, creating a space where they share best practices and support specific lines of work.

Table 35.2 Two telemedicine technologies and comparison

Type	Store-and-forward	Two-way interactive
Situations used	Nonemergent	Synchronous, often urgent or in postoperative follow-up
Present uses	Teleradiology, ultrasonography, telepathology, teleanesthesia, teledermatology	Real-time videoconferencing for patient consultations using otoscopes, stethoscopes, or presence of visiting nurses
Advantages	Requires less bandwidth	Real-time
Disadvantages	Takes longer	More expensive, requires more bandwidth

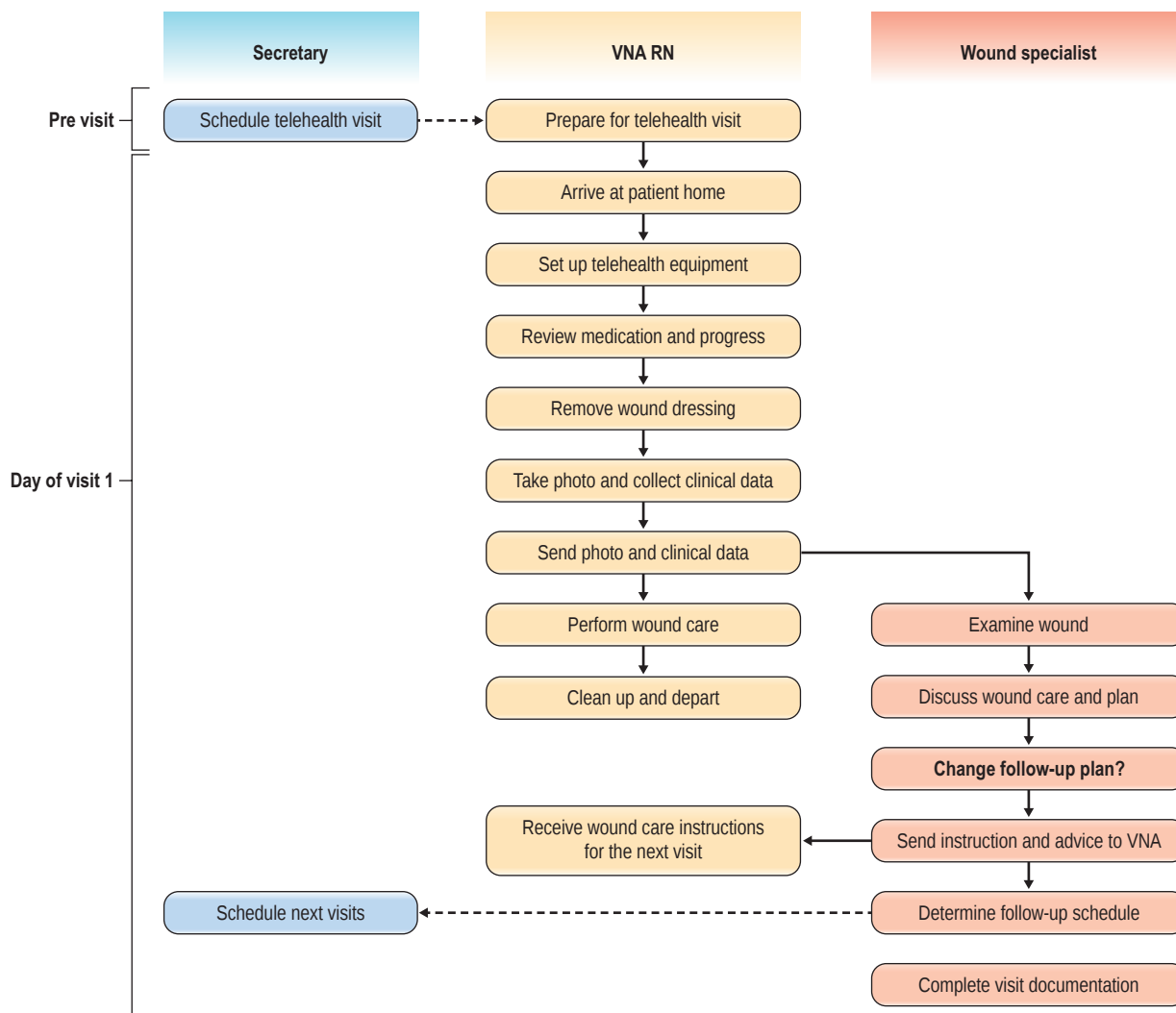


Fig. 35.10 Wound clinic telehealth “store-and-forward model” timeline. The secretary who schedules the visit communicates with a registered nurse (RN) from the visiting nurse association (VNA) to help plan and conduct the visit. The nurse then confers with a wound specialist to examine and treat the wound, and communicates back to the secretary to close the loop.

Plastic surgery and telemedicine

Plastic surgeons have used telemedicine predominantly in communicating about individual cases in the international medical arena. Telemedicine can be used in the preoperative, operative, and postoperative phases of a plastic surgical operation. Through organizations such as ReSurge International, plastic surgeons anywhere in the world receive daily updates about cases in developing nations where consultations are requested.³⁴ These surgeons can choose to log on to the online system to provide their expertise on the case. They can view patient diagnostics and past medical history, and write a case report. This is a prime example of medical care at a distance.

The other major area in which telemedicine impacts plastic surgery is in telesurgery. Using telesurgery, surgeons can operate on patients who are geographically remote: for example, a patient who cannot physically or financially afford to travel to the doctor.³² In the future, surgeons might remotely operate on an injured soldier on a battlefield,³³ or a victim of an earthquake, hurricane, pandemic, or other disaster (Figs. 35.14 & 35.15). One major advantage of telesurgery is that patients can remain in their own environ-

ment, where they can receive care and support from community or family members.

A brief description of the specific “tele” terms relating to telesurgery may help the reader. The term teleoperation means doing work at a distance. Telesurgery refers to doing surgery across a distance. For example, a surgeon, in one location, can control a surgical robot at a remote location (known as telerobotics). Telerobotics is depicted in Fig. 35.14 with a schematically drawn robotic surgeon; though in practice, a telerobotics system might look more like the da Vinci system (Fig. 35.16), with the surgeon using a control console and viewing system at his or her site, directing the actual operating robot at a remote site, which must also have a camera to send back images to the surgeon of the robot’s-eye view. Telepresence refers to being somewhere one is not physically present: the best current example is videoconferencing, which makes one “present” via two senses: sight and sound. In the surgical example, telepresence could mean an expert surgeon projecting his or her image into a remote operating room, via two-way videoconferencing, to be a mentor assisting the other surgeons in real time. The OR surgeon(s) would see the remote mentor “appearing” on a

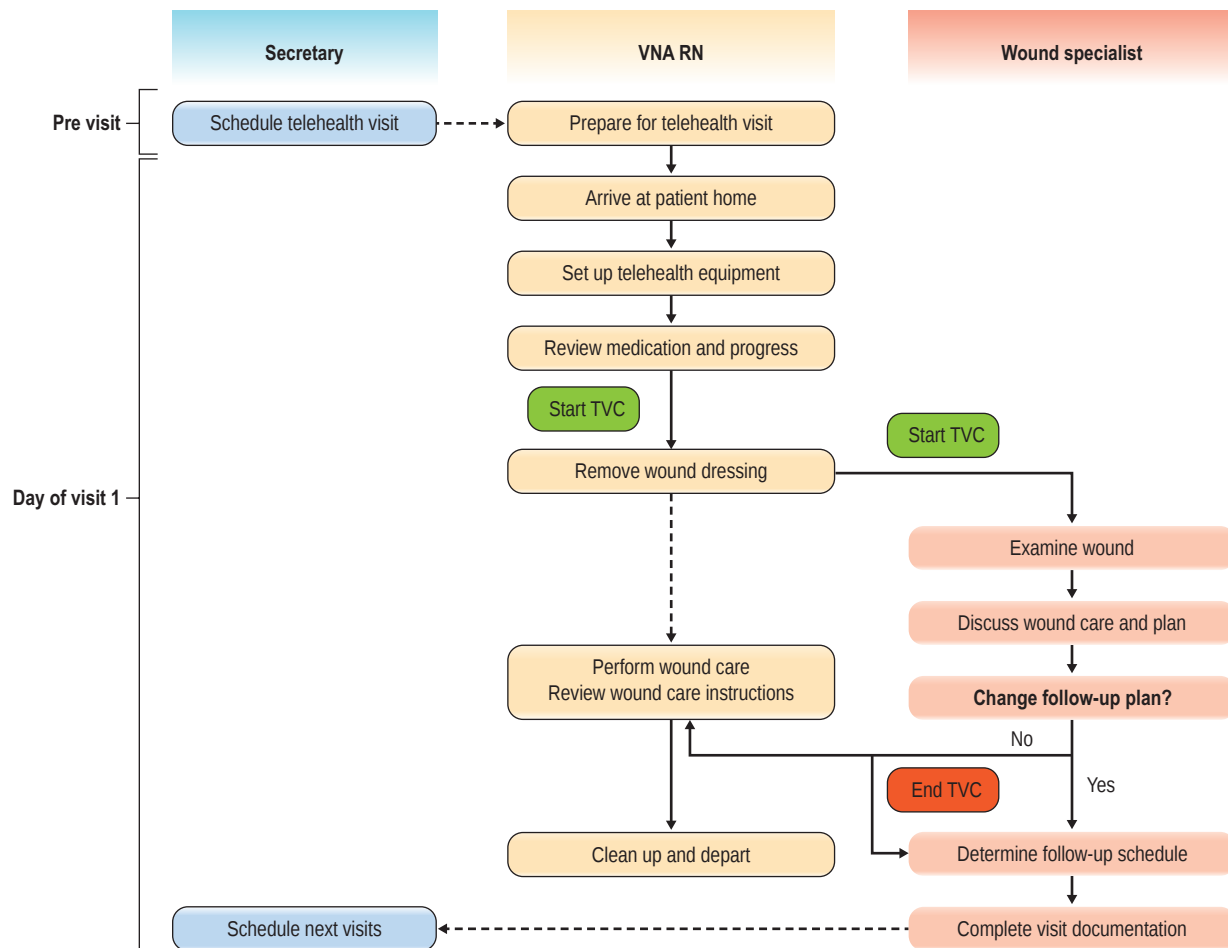


Fig. 35.11 Wound clinic telehealth “synchronous model with video conferencing” timeline. This scenario is similar to Fig. 35.10 where the secretary communicates with the registered nurse (RN) at the visiting nurse association (VNA), who in this case conducts a telemedicine video consultation (TVC) to communicate with the wound specialist.

monitor in the OR, and the mentor would likewise see an image of the OR and surgical field. Virtual telepresence could also be employed, in which a computer-generated surgical mentor (perhaps from an animation or a simulator) would project into the actual OR to help instruct the surgeons (see Fig. 36.14).

Telemedicine for the plastic surgeon

Each state is adopting or creating its own regulations to monitor and establish telemedicine practice. Physicians using telemedicine must be licensed in the state of their established practice and the state where the patient is located, if different.



Fig. 35.12 Telemedicine postoperative consult. (Courtesy of Dartmouth-Hitchcock/Mark Washburn.)



Fig. 35.13 Telemedicine postoperative at-home consult. (Courtesy of Dartmouth-Hitchcock/Bonnie Barber.)

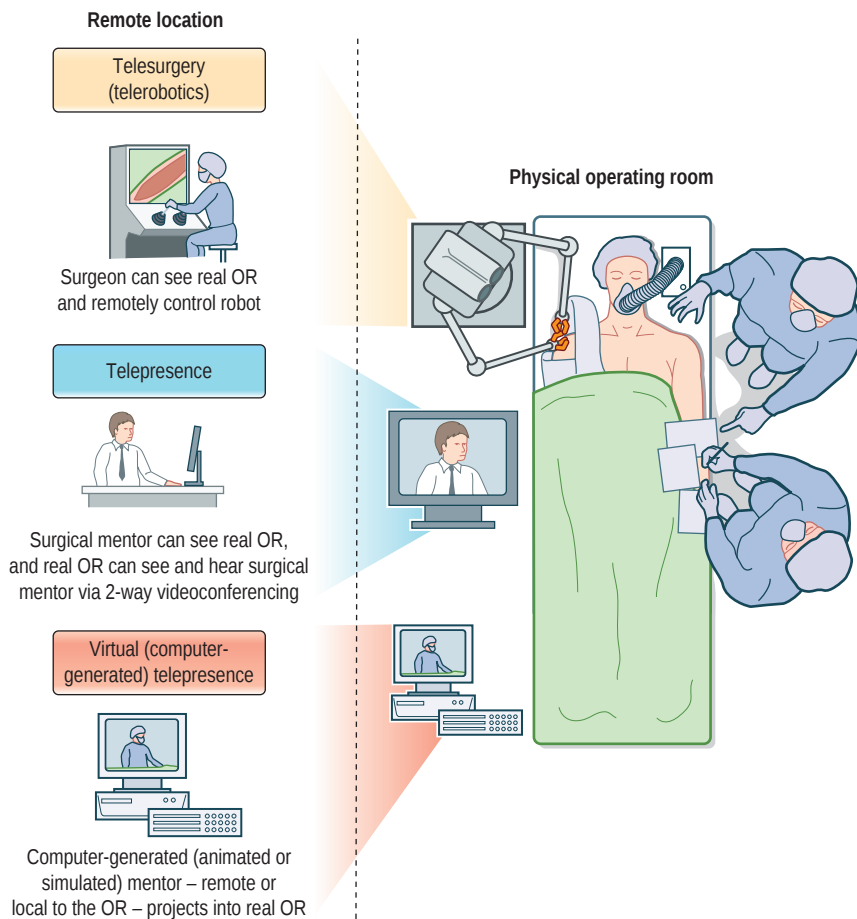


Fig. 35.14 Telesurgery and telepresence are two ways in which a remote surgeon can assist in, and/or direct procedures in, an operating room (OR) anywhere else in the world. In telesurgery, the remote surgeon controls a robot that actually conducts the surgery. In telepresence, the remote surgeon serves as a mentor to instruct the surgeons in the actual OR, using two-way videoconferencing (alternately, a computer-generated, animated or simulated surgical mentor is projected into the actual OR). In both telepresence and telesurgery, the remote surgeons see a view of the actual OR with images collected by camera and transmitted in real time.

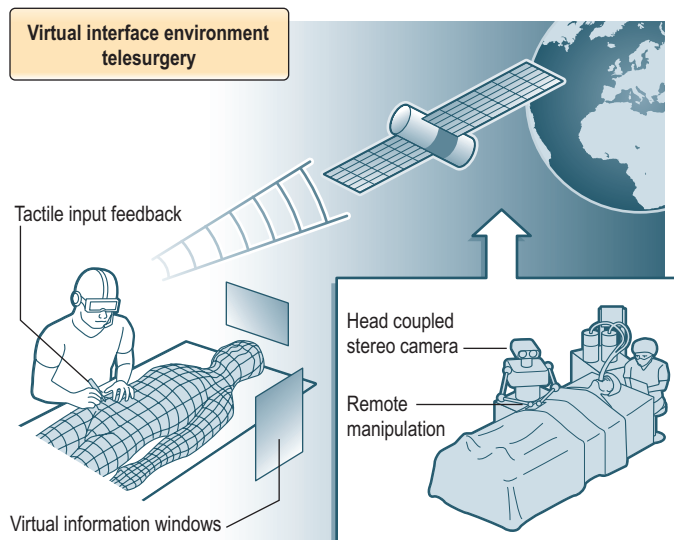


Fig. 35.15 Telesurgery via satellite using haptics and robotics. Image depicting conceptualization of how surgeons might someday conduct surgery from Earth to space. (Courtesy of Joseph Rosen, MD.)

Nationally, the American Medical Association's Code of Medical Ethics has been challenged to include telemedicine because of a key issue: does telemedicine allow for a patient-physician relationship? The current law in New Hampshire allows physicians to establish a patient-physician relationship and prescribe medications via telemedicine. Prescribing drugs without such a relationship is not allowed, except under certain conditions, including newly hospitalized patients. Most controlled substances may not be prescribed by telemedicine.³⁸

Ubiquitous mobile telemedicine

There are significant barriers to overcome before telemedicine can be incorporated ubiquitously. We must demonstrate its cost-effectiveness; resolve insurance reimbursement issues; resolve legal issues regarding licensing of physicians working across state and international lines; and provide sufficient internet connectivity and bandwidth. Telemedicine technology will be important in the ongoing healthcare debate, as it promises to provide a potentially higher quality of care at a decreased cost.

Telemedicine has the potential to transform the role of the plastic surgeon as a provider, by making access to care both cheaper and faster as part of a networked healthcare system. Providers will not have to receive teleimages over email or be physically present in a room with expensive video conference

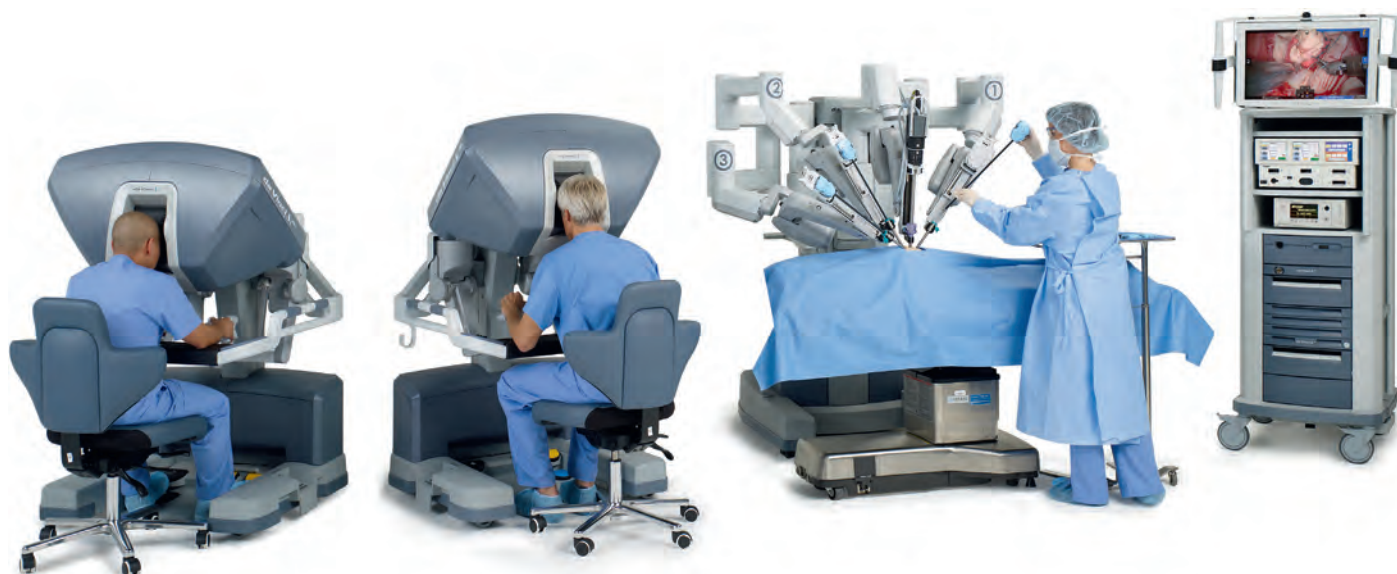


Fig. 35.16 da Vinci Si high-definition robotic surgical system, showing two surgeon consoles, patient cart, and vision cart. (Courtesy of Intuitive Surgical and © 2012 Intuitive Surgical, Inc.)



Fig. 35.17 Smartphone medical applications. (Courtesy of Joseph Rosen, MD.)

equipment, but will be connected to a network through mobile handheld devices that allow them to acquire data and diagnostics about a case, formulate a patient plan, supervise surgery, and perform consultations in real time.

Technological convergence

The reconstructive ladder for the 21st century is one in which the plastic surgeon is able to weigh the risks and benefits associated with fixing a deformed limb or face with many choices: through reconstructive surgery, using microsurgical techniques; or through replacement using either robotic prostheses, a human tissue transplant, regenerative medicine, or tissue engineering.

Diagnostics, therapeutics, and networking are all being supported by robotics, simulation, and telemedicine. These technologies depend on information technology/information management bandwidth, speed and processor power, all of which will become better, faster, and cheaper. Given the wide use of smartphones and the abundance of medical “application” development, patients, physicians and plastic surgery trainees can explore different aspects of healthcare at their fingertips (Fig. 35.17). The website, iMedicalApps.com reviews medical “apps” and telemedicine technology that are at the forefront of innovation.^{39,40} The developers of iMedicalApps.com have since developed iPrescribeApps.com, a website that can allow physicians to prescribe an app for patient use.^{40,41} We will be able to make diagnostic decisions from smaller and smarter devices, linked to a larger network, and these devices’ capabilities will increasingly converge. It is now possible to access the *Plastic and Reconstructive Surgery Journal* from a desktop computer, laptop computer, and even an iPhone or Android device. In the future, it will be downloadable on an iPhone and viewed remotely while participating in telemedicine over the phone or another handheld device.

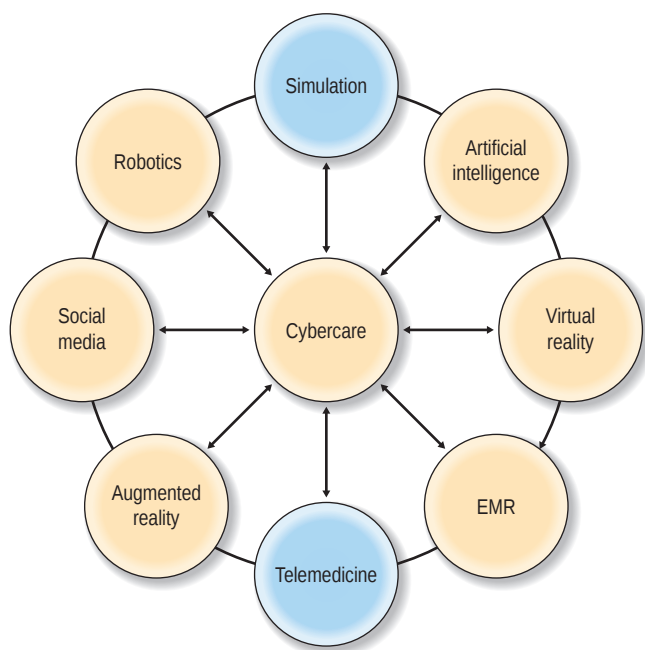


Fig. 35.18 Healthcare of the future as a network centering on Cybercare development. EMR, electronic medical record. (Courtesy of Joseph Rosen, MD.)

Conclusion

Over the next ten years we will see a dramatic reduction of cost in information technology and a steady increase in computational power. This will result in a significant improvement in the ease of using these technologies in our practices. Information technologies will take many forms, from the two that we have just discussed, simulation and telemedicine, to many others. We use the term “Cybercare” to encompass the many different information technologies in medicine that will impact plastic surgery (Fig. 35.18).

At present, each of our practices and institutions are incorporating electronic medical records. These initial systems have created significant barriers to our practices with respect to cost and time. In the future, these information systems will incorporate both simulators and telemedicine. They will also incorporate intelligent agents and artificial intelligence to improve our ability to do our jobs and increase our safety. Intelligent agents can be incorporated within these systems to follow a lab value and make sure that we see this result and respond to it in an appropriate manner. Artificial intelligence can aid us in making the right decision about which antibiotic to use, and make sure that we do not give the wrong

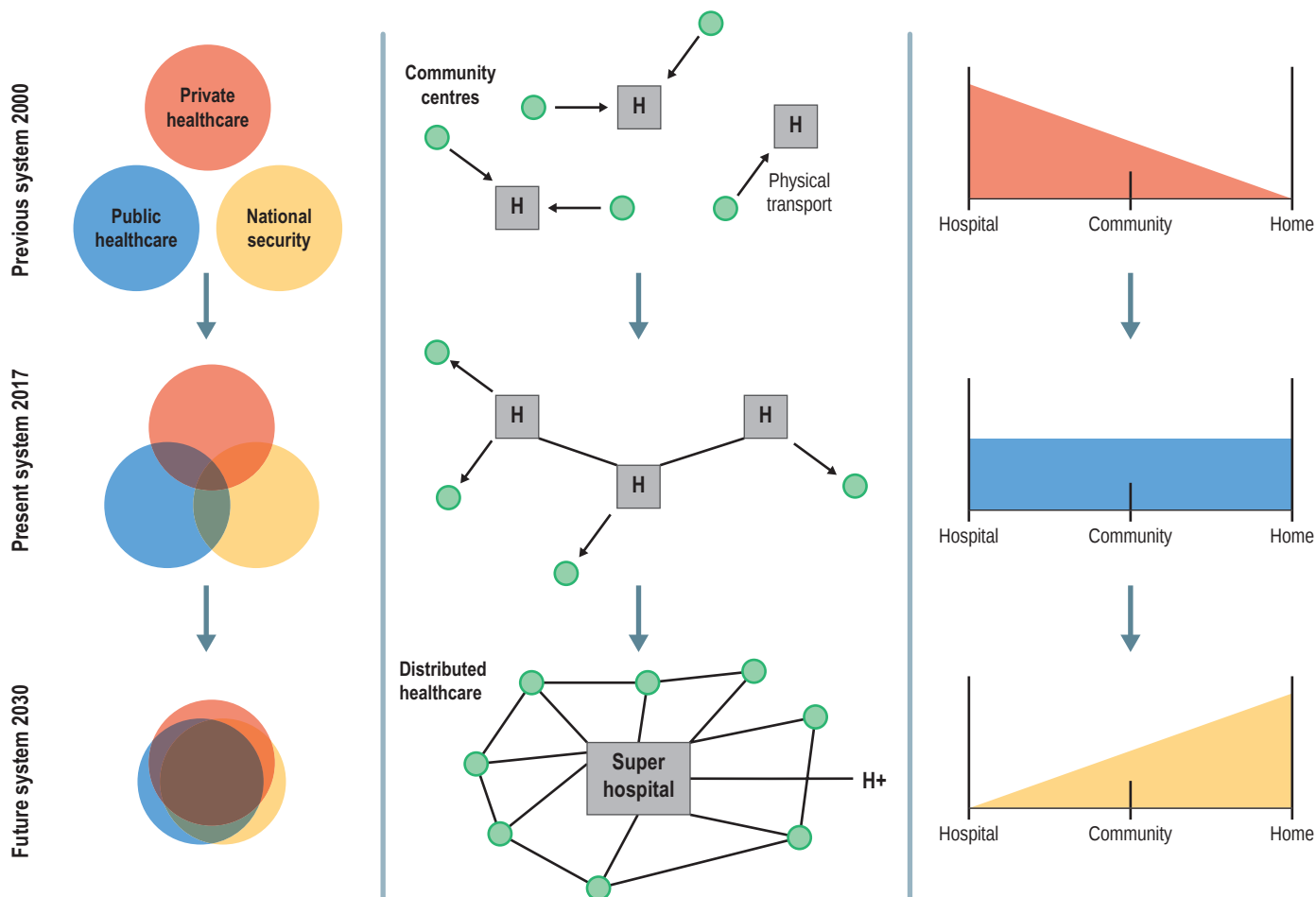


Fig. 35.19 Evolution of healthcare from hospital-centric to user/patient-centric network. (Reprinted with permission from Rosen JM, et al. *Cybercare 2.0: meeting the challenge of the global burden of disease in 2030*. Health Technol (Berl). 2016;6:36.)



Fig. 35.20 The clinic visit of the future where the patient and the physician can visualize and interpret medical records via virtual reality lenses. (Reprinted with permission from Rosen JM, et al. *Cybercare 2.0: meeting the challenge of the global burden of disease in 2030*. Health Technol (Berl). 2016;6:36.)

medication to a patient who may have an adverse reaction to that drug. For example, Watson by IBM is challenging how we diagnose and treat cancers.⁴²

Our practices will shift from the hospital to clinics to the home. Plastic surgery has been the leader in providing high-quality surgical care in an outpatient setting. This trend will continue. And instead of the patient coming to the hospital, information and decision-making will shift from the hospital to the clinic to the home (Fig. 35.19). Care will follow a network and patients will share information on social media and the internet. This should result in improved care at a decreased cost. A physician can provide care anywhere within

this network through telemedicine, by phone, by teleconference, by wearing a virtual reality interface, or by being within a virtual reality WAVE (see Fig. 35.7).

The physician of the future may see a patient using a virtual reality interface, like Google Glass. When additional information is provided through this interface, we call it augmented reality (Fig. 35.20). This will provide additional information about the patient from the electronic medical record, outside records and up-to-date literature. And at the same time the patient can wear an interface to help them to better understand the planned procedure. The patient interface could have a simulation of the procedure that explains the procedure to the patient step-by-step.

Over the next ten years, the delivery of healthcare and plastic surgery will be transformed by information technology. It will take many forms, and it will have a learning curve that each provider will face, but eventually there will be an improved system that provides better outcomes for the patient with increased safety.

Acknowledgments

We also wish to extend thanks to the various doctors and product developers who helped review the chapter and provided comments, content, and images.



Bonus images for this chapter can be found online at

<http://www.expertconsult.com>

Fig. 35.1 Early surgical planning using modeling clay for nose flap. (Courtesy of Joseph Rosen, MD.)



Access the complete reference list online at <http://www.expertconsult.com>

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Digital technology in plastic surgery

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Introduction

Advances in digital technology have impacted and will continue to impact plastic surgery. This chapter will explore the effects of current and future technology on the patients' and doctors' experiences: (1) prior to the plastic surgery consultation, (2) during the patient encounter(s), (3) in the operating room and during the perioperative period, and (4) during long-term follow-up. The chapter will also discuss the impact of digital advances on education, research, medical devices, patient monitoring, "Big Data" analytics, and registries.

Digital technology before the first consultation

Introduction

Digital advances have expanded the base of knowledge available to patients such that even before consulting with a doctor, patients can become well informed about procedures, the selection of available surgeons, and the methods used to make an appointment. A plethora of informational websites are available to educate patients on procedures, postoperative recovery, surgical limitations, and other information needed to ensure the patient arrives at the consultation prepared and knowledgeable.

Information on procedures

Using online databases and websites, patients can learn more about the procedures they might undergo before speaking with a physician. Informational websites and applications can allow patients to compare and differentiate between various procedures. By examining the descriptions and exact procedures of different operations, patients can analyze the inherent risks and dangers. Websites such as www.smartbeautyguide.com can aid patients in choosing a procedure, understanding

potential complications, and even finding a surgeon whose office is geographically convenient to the patient. The availability of this information can produce a more informed patient and a more efficient and effective consultation with the plastic surgeon. Some applications allow the patient to visualize simulated results through 3D animation and may produce full 3D models through the interpolation of several 2D pictures, which can be uploaded by the patient to the website before seeing the plastic surgeon. The patient must visit the physician to see the 3D images. Online content on plastic surgery websites often includes animations designed to educate patients on the conduct of surgical procedures in an abstract manner for those who may not be able to tolerate video content documenting real surgery.^{1,2} For patients seeking more detailed video content on planned procedures, many surgeons create custom video content and post it to YouTube.com or other sites, along with links from the surgeon's website to the videos.

Plastic surgeons can also permit prospective patients to access certain office documentation to save time in the office for both patients and the surgeon's staff. These documents may include office policies and procedures, general consents to treatment, HIPAA privacy notifications, Patient Bill of Rights documents, intake questionnaires, menus of services, pricing lists, surgeon biographies, procedural brochures, financial policy disclosures, and others. By having prospective patients fill out these forms online or print them out and bring to the visit, the intake process at the initial consultation becomes more streamlined and more efficient for all involved. Consequently, the patient may arrive for a consultation having extensively researched the plastic surgeon's practice and the local marketplace dynamics, prepared with preliminary forms and materials, and armed with numerous questions and an idea of what he or she desires.

Choosing a surgeon

Patients considering plastic surgery can search the internet for detailed information on surgeons and their practices, their

credentials, price estimates for procedures, patient satisfaction testimonials and outcomes culled from review sites, and galleries of preoperative and postoperative photos.

Patients often research a plastic surgeon's credentials and reputation before choosing a surgeon by reviewing the practice's website as well as a number of review sites.³⁻⁷

These sites not only provide patients with a forum to share their perceptions of the quality of the surgical outcome, but also the quality of customer service, the appearance of the office, and the friendliness of the staff, etc. These sites can give patients significant influence on the reputation of the doctor or practice, which can be detrimental or advantageous. However, the entirety of the surgeon's online presence including videos, media appearances, blogs, Facebook, etc. help to shape the surgeon's and practice's brand⁸ and, thus, it is important that the surgeon continually monitor his or her presence on the web either with a third-party service or by setting targeted Google alerts.

Patients may seek procedure pricing information to comparison shop among practices by soliciting online fee schedules and can compare menus of services where available. This information is occasionally available directly on a practice's website or can be explored on specific apps and portals.⁹ One study demonstrated that patients were more likely to book surgery at the time of the initial office visit if they knew the price of the procedure before arriving for the consultation.¹⁰

Patients can also evaluate a surgeon's results by evaluating before-and-after photos that the surgeon displays online. These galleries of before-and-after photos provide real examples of the surgeon's work and are often categorized by body location and procedure. Some programs¹¹ allow galleries to be accessed only via a password-protected patient portal that requires prospective patients to register before being

granted access (Fig. 36.1). Photo galleries can represent a meaningful component of plastic surgery marketing while also serving an educational purpose for the public. Some plastic surgeons who do not favor placing patient photos online nonetheless may provide guidance to prospective patients to contact the office for an in-person consultation, where these photos, deployed either in bound albums or using digital tools (tablets, large screens in viewing rooms, waiting-room results reels in PowerPoint presentations), are available for viewing in a controlled environment.

After selection

Once a patient has selected a plastic surgeon's office for a possible consultation, the online experience can be augmented with real-time chat tools on the surgeon's website and calendar integration via sites that permit the patient to find open appointment timeslots in the surgeon's office schedule and book visits online, with the appointments automatically populating the office practice management software system¹² or via the patient portal of some electronic health records (EHRs) with this capability.¹³ Voice-over-Internet-Protocol (VoIP) systems allow offices to communicate with patients even asynchronously to open office hours, from most mobile devices and from most locations, obviating the need for fixed landline telephone systems. Online maps with directions shareable to mobile devices or in-dash navigation systems in automobiles streamline the process of finding the doctor's office, with dynamic updates on traffic patterns available in apps like Waze (now a part of the Google Maps toolkit).

Patients wishing to travel for surgery and those who have limitations on the ability to see a physician in the office during convenient office hours may benefit from applications

Demo Cosmetic Plastic Surgeon

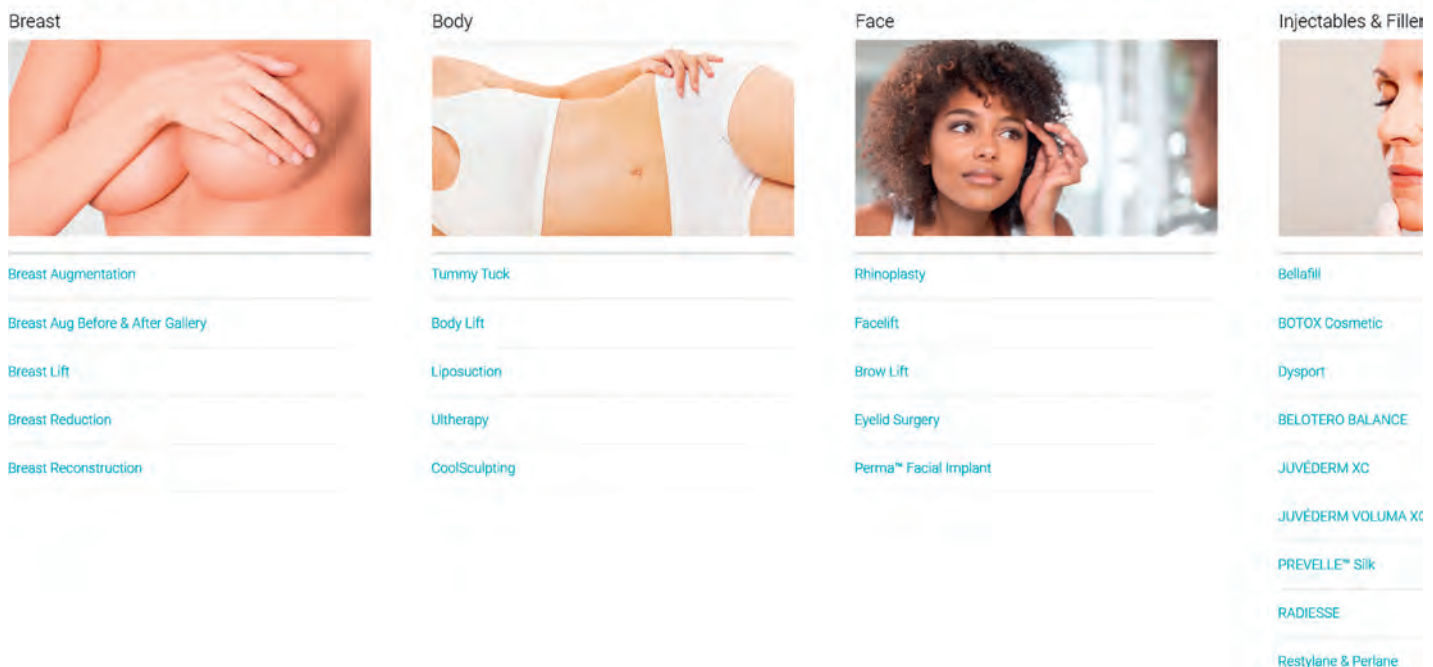


Fig. 36.1 Menu screen of the patient portal allowing access to educational content and before-and-after galleries in a password-protected patient portal that the patient can review with any internet connection. (© 2015 TouchMD, an ALPHAEON Company. Used with permission. All Rights Reserved.)

that facilitate virtual consultation.¹⁴⁻²¹ One Harris poll commissioned by a prominent telemedicine vendor in 2014 indicates that 64% of consumers are willing to see physicians via video consultation.^{22,23} The Federation of State Medical Boards has issued model legislation aimed at encouraging standards in the credentialing and licensure oversight for providers of telemedicine services in participating states.²⁴ Some states do not permit telemedicine consultations, and insurance reimbursement models and legal considerations are undergoing significant debate. Nonetheless, the promise of mobile technologies in the field of telemedicine is substantial and in 2013, three companies alone hosted 400 000 to 500 000 doctor–patient interactions.²⁵ For the plastic surgeon, there are opportunities to potentially rule out poor candidates for surgery before they incur the expense of traveling to the surgeon's office, or to permit office staff to begin the intake and preoperative workup process for remote patients, or to provide a more personal introduction as part of marketing outreach to bring in more patients.

Patients who require urgent but non-emergent care (for example, for minor burns or other minor trauma) also have tools for finding local clinical resources via applications similar to “sharing economy” tools like Uber. Some innovative apps²⁶⁻²⁸ provide logistics for connecting patients with available providers on demand, creating a digital platform to reimagine the “house call” of old, or allowing patients to bypass costly points of care like emergency rooms and arrange services in the office.²⁹

Digital technology during the office visit

During the consultation encounter, digital technology can enhance: (1) patient information gathering and archiving in the form of electronic medical records including patient data, medical information, photographs, and documents; (2) patient education via digital materials; and (3) clinical information and decision-making.

Medical records

Choosing an electronic health record (EHR)

The Health Information Technology for Economic and Clinical Health (HITECH) Act, enacted as part of the American Recovery and Reinvestment Act of 2009, was signed into law on February 17, 2009. Starting in 2011, eligible professionals could receive incentive payments up to a total of 5 years if they could demonstrate “meaningful use” of certified electronic health records (EHRs). Providers faced up to 5% penalties if they did not demonstrate meaningful use beginning in 2015. As a result, adoption of electronic health records increased during this time.³⁰⁻³⁴ Even plastic surgeons who do not treat many Medicare patients have increasingly adopted electronic health records and practice management software. The EHR market continues to evolve. The market is anticipated to consolidate, as rules, regulations and functionality demands increase in this space. However, many EHRs were designed with the primary care physician in mind and thus can be lacking in key features desired or required by the average plastic surgeon. In addition, many programs require a significant upfront investment of

both time and money. Physicians and office staff may experience challenges in implementation and training with new EHR systems, sometimes with a considerably steep learning curve, requiring significant allocation of staffing time before the EHR is fully operational for the office's needs. Thus, the choice of EHR can be crucial. Below are some key considerations regarding the EHR itself that should be taken into account when choosing an EHR system.

Certification

Determining whether the chosen EHR is certified by the ONC (Office of the National Coordinator of Health Information Technology) is important, especially if the plastic surgeon is planning on participating in certain government incentive programs. Certification is meant to assure that the EHR system offers the capability, functionality and security to meet the Meaningful Use (MU) criteria established by the Centers for Medicare and Medicaid Services (CMS).³⁵ The Meaningful Use program is in the third of three “stages” of implementation along an 11-year timeline (culminating in the final Medicaid incentive payments being slated for 2021), with penalties to be levied against practices which see significant Medicare or Medicaid volume and fail to demonstrate compliance with MU. Certification provides one level of reassurance that the EHR system allows entry of data necessary to achieve MU compliance and is a toolkit for submission of reports to CMS for validation and incentive processing. For plastic surgeons not interested in participating in the Meaningful Use program, certification may provide some level of assurance that the program meets certain standards of functionality, security, and interoperability, and probably is more likely to survive consolidation than other non-certified programs.

Server on site or off site or subscription model (SAAS – Software As A Service)

There are three principal models through which an EHR program can be provided to users. Some EHR vendors can be deployed all three ways. The most traditional model of software delivery houses the program and data on a server in the office owned by the physician/group. The physician has complete control of the data, but is responsible for hardware maintenance, back-ups, insurance, and security, as well as manual updating of the software. Access from a remote location or satellite offices is also maintained by the physician's practice, and may involve high-speed data access lines (T1 or fiber-optic cable, for example), virtual private networks (VPNs), and other remote logging programs. This model may require higher upfront costs for hardware infrastructure and, depending on the size of the practice, one or more IT specialists outsourced or employed in-house. Another model involves using a server that is housed off-site, maintained by a third-party vendor. The physician/group still maintains complete control of the data but leases space in a remote server. Updates frequently still require manual effort, but responsibility for servers, back-ups, and insurance is assumed by a third-party vendor.

Finally, the Software-As-A-Service (SAAS) model is a subscription service in which the program and data are maintained and updated by the EHR vendor, with the software accessed via the computers/devices in the practice – much like the way Gmail, Yahoo! Mail, Dropbox, and other online programs

work. The updates are usually real-time and performed automatically by the EHR company, often without disrupting the software's availability. The server function, back-ups, and security of the server is assumed by the EHR company. Depending on the contract, the physician/group may incur fees to have the data extracted into a usable format when changing vendors. Some contracts and user licenses permit the EHR company access to or ownership of the data. In some cases, de-identified data (records that have been stripped of identifying personal or demographic information) can be used by the vendor for purposes of research, product development, or aggregation and commercialization. This model usually boasts lower upfront costs for hardware purchase and installation, and delivery through a cloud infrastructure facilitates easier access from remote locations and satellite offices. Increasingly, both professional and consumer software is being delivered through the SAAS model, with support, training and updates bundled into the subscription costs and availability provided "anywhere, anytime and on any device".

Stability in the market

A search of the ONC-approved comprehensive EHR list as of 2015 shows 648 approved programs,³⁶ a number that is probably unsustainable. Even in 2012, 75% of users of EHR products were concentrated among the top 6 vendors serving hospitals and the top 15 serving outpatient venues.³⁷ Accordingly, an important consideration when choosing an EHR is whether the product is anticipated to survive an expected consolidation of the market among sustainable leading vendors. Such vendors often have the advantages of consistent revenue from the installed user base along with scalable physical and human resources that may allow them to fulfill further governmental or other regulations better and to make updates and improvements to their programs. On the other hand, larger EHR companies may be somewhat less responsive to suggestions by users to improve the usability or functionality of their programs or to add features that are crucial to only a small subset of their users. As plastic surgery is a relatively small specialty, this can sometimes be an issue impeding the timely selection of an EHR with essential features needed by the average plastic surgeon.

Features and functionality

Most certified EHRs can adequately accomplish the generation of a satisfactory progress note, problem list, medication list, etc. More important is the ease of use of the software. The usability of many programs is hampered by the requirement for multiple clicks, non-intuitive navigation, and a cumbersome maze of windows and menus. It is critical to request a detailed demonstration of the functioning program and to engage with current users of the system who are reference clients of the vendor. One way to accurately experience the ease (or difficulty) of use and functionality is to have the demonstration performed in a manner that follows the practice's current workflow from initial patient contact, scheduling, registration, intake, note generation, billing, reporting, follow-up, etc.

As discussed above, many EHRs in the market were not designed with plastic surgeons in mind. Practices should carefully vet those features that may not be accessed by a general provider, including cosmetic quote generation, inventory and

point of sale management of product lines, prepayment for services (e.g., deposits and prepayment for cosmetic surgery or package pricing for lasers, etc.), photo archiving with rich search and display features (see below), patient management (see section below), and others. Contracts and user agreements that are contingent on the development or enhancement of a feature or functionality should have clearly agreed-upon language in the contract with timelines and benchmarks, along with consequences for missed milestones.

Support and implementation

Implementation, training and support are critical services provided by vendors. Important considerations include the length, complexity, cost and responsibilities for the installation process as well as the amount of initial and ongoing training included and available. Guaranteed limits on outages and unavailability of the software during updates, bug fixes and other interruptions should be sought and practices should seek clear terms regarding the support resources available in such instances, especially after normal business hours. Even something as seemingly trivial as the time zone of the vendor's support headquarters may have an impact on office productivity if the practice experiences bugs, slow data processing, access problems or other issues during normal business hours in another time zone. Many vendors provide extended hours or offer "premium" support (typically at a surcharge) to cover such contingencies. Most experts recommend that a busy practice anticipate a decrease of 50% in both productivity of office staff as well as physician volume during the implementation period of the EHR (which in some cases can last months to a year or more).³⁸ One study estimated an average of 611 hours required to prepare for implementation of the EHR, and 134 hours needed by end-users (physicians, clinical and non-clinical staff, etc.) to become sufficiently familiar with the EHR system to feel comfortable using it regularly with patients.³⁹

Contracting considerations

As with most contracts, it is advisable to have an attorney familiar with such transactions review the EHR vendor's contract, including (where appropriate and provided) Master Services Agreements, Statements of Work, and User Agreements/Terms of Use. Some specialty society and state medical societies also offer resources on this topic. Some basic considerations to delineate include:

1. Who owns the data?
2. Does the contract grant the EHR company permission to access the physician's patient data and, if so, is it in a de-identified and aggregate form and is the company permitted to sell the data to other parties?
3. Is there a required duration of contract? If so, what constitutes a breach of contract to allow the physician to terminate the agreement early (e.g., excessive downtime, lack or loss of certification by ONC, failure to create agreed-upon features, etc.)
4. When the physician changes vendors, what is the process to decrypt the data and provide it into a usable format such that it can be used in another EHR? What is the cost of the data conversion and agreed-upon timeline and redress for failure to deliver the data in a timely fashion?

5. What is the process to gain support for downtime of the program? There should be a maximum percentage set for downtime and a maximum time for resolution.
6. Is there an agreement to work with other vendors to allow for interfacing or integration of different programs (e.g., photo archiving or morphing programs, patient management systems, third party billing clearinghouses, etc.)?
7. Are there additional costs to add providers, support staff or satellite offices? Some EHR programs charge per user, others per physician (or provider, including nurse practitioners and physician's assistants), still others per computer terminal workstation license.
8. Who is responsible for installing and ensuring the functionality of the EHR program?
9. What capabilities exist for interoperability of systems – i.e., does it link to laboratory vendor data, radiology systems (PACS or DICOM viewers), other EHRs, etc., and is there an implementation or maintenance cost for these services?

Using the EHR

A comprehensive primer on the use of EHRs is beyond the scope of this chapter. However, this section illustrates some suggestions to help enhance the effective use of EHRs in a plastic surgery practice.

Intake and entry of information via patient portals and on site

ONC-certified EHRs are required to furnish a patient portal that allows patients to access limited portions of their medical record and results as well as interact with the office. Patient portals which allow the patient to enter demographic and clinical information prior to the office visit can improve office efficiency by minimizing the amount of data entry at the time of the visit. Some programs allow different questionnaires and intake documents to be created which can be tailored to specific physicians' practice preferences, or keyed to the patient category (e.g., the surgeon is likely to be interested in different information when seeing a hand surgery patient vs. a facelift patient). Demographic entry by patients permits them to update contact information and privacy permissions in a more timely and well-documented manner. Alternatively, such intake forms can be completed in the office with staff members assisting the patient with the appropriate electronic forms or performing a transcribing function for patients who have difficulty working with digital devices. Bubble forms (similar to Scantron standardized test forms but printed by the practice on regular paper) can be created and used in some EHRs^{40,41} which scan the responses into digital format directly into a progress note. Advances in optical character recognition (OCR) and natural language processing (NLP) are likely to further enhance the intake of medical information into structured medical records.

Data entry at the time of the patient consultation

Copious entry of free text at the time of the patient consultation is neither feasible nor desired. Typically, EHRs make use of a library of templates created for various patient encounters, e.g., initial breast reconstruction consultation, breast

augmentation consultation, tissue expander visit, encounter for injectables, etc. Most EHRs permit the templates to include not only the current chief complaint(s) and history of present illness with associated relevant physical exam, but also the typical discussion, treatment plan options, orders, and medical coding. These work best when there are visit categories which are more frequent for the practice, and some EHRs will build these templates at the time of implementation based on the practice's current EHR documents or paper forms being used in the practice. Certain visits might best be recorded with a visual form or on anatomic images, with annotations typed or drawn as appropriate, as is commonly done when recording injection sites for botulinum toxin and filler treatments. It is important to assess whether the EHR allows the physician or other user to create custom templates to fit the practice's regular workflows or the user's personal preferences, as opposed to requiring that requested changes or templates be submitted to the EHR company. Customization can be key to effective use of an EHR system.

With less common or complicated encounters, templates may be less helpful as real-time text editing becomes necessary. Some physicians find it helpful to enter prelim summary notations to be further clarified after the patient encounter, with the note being text-edited at a later date or the provider utilizing speech-to-text transcription in a program like Dragon Medical. Some surgeons prefer to utilize medical scribes who can enter all the appropriate information at the time of the encounter, recording observations rapidly into the EHR while the physician focuses on direct patient care and face-to-face interaction. The scribes can be the physician's employees physically present in the examination room, or may be at a remote location. One vendor¹¹ offers HIPAA-compliant scribing services via Google Glass technology, allowing the scribe to see and hear the patient encounter while transcribing from a remote location. Newer EHR products are leveraging the widespread availability of mobile technologies and Wi-Fi to facilitate less disruptive ways to use an EHR in the patient encounter (Fig. 36.2).

Alerts

Many EHR products also allow custom setting of alerts to assist with clinical decision-making or with business practice.

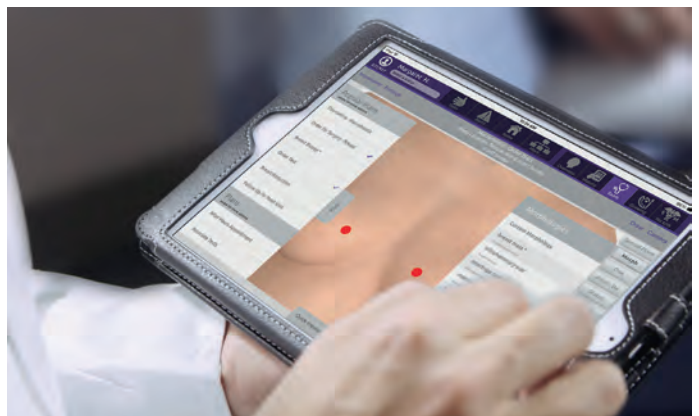


Fig. 36.2 Modernizing Medicine EMA Plastic Surgery. (© 2015 Modernizing Medicine, Inc., used with permission. All rights reserved. Modernizing Medicine and Electronic Medical Assistant are registered trademarks of, and EMA is a trademark of Modernizing Medicine, Inc.)

For example, some systems allow the user to set an alert which pops up whenever a specific patient chart is opened to display, for example, that this patient needs to retake her photos or pay for her most recent treatment. Most EHRs also provide alerts for medication contraindications, drug–drug interactions, and/or disease process considerations when prescribing medication. Some programs may allow the user to customize action items that only display when specific criteria are met. For instance, if a female patient is older than 50 years old and has not had a mammogram in the last year, the EHR may prompt the user to consider ordering a mammogram, and may even provide computer provider order entry that generates a printable requisition or transmits the order electronically to a radiology center.

Document and forms management

Most EHRs enable the user to upload forms that are required by various vendors and facilities, such as the OR scheduling sheet at the surgeon's local hospital or the order form for a frequently prescribed product or durable medical equipment. Some EHRs will allow the user to mark directly on the image of the form and save it as a document. Others will also allow the form to be set up to capture each blank in a form as structured data (e.g., smart PDF forms) that can later be used to generate reports or used in a mail-merge document.

Integrated systems

As much as possible, arrange for integration of the various programs that will be used in the practice. Many vendors of EHR products now offer integrated software suites that include medical records, billing, practice management, laboratory and diagnostic study results, revenue cycle management, inventory, operating room compliance documents, consent forms and surgical quotes. These systems may also feature direct data integrations or single-sign-on interfaces to the products of other vendors. For instance, a vendor of an EHR which does not offer a practice management module may nonetheless build “data bridges” to commonly used practice management software products, allowing practices to mix and match products that may better suit the practice's needs, budget, and profile. Not uncommonly, one EHR product may not fit all the needs of a practice, and a separate photo management product (see below), patient education system (see below), or digital simulator program may be desired. Ideally, these should also be integrated as much as possible, even when provided by competing vendors. Integration reduces the requirement for double or triple entry of patient demographics in each program and can obviate the need to open multiple screens and programs with different sign-ons and user interfaces. One positive result of the more widespread adoption of EHR programs among physicians and hospitals is the potential (although as yet unrealized) promise of long-needed progress in interoperability among multiple vendors of medical record and other health information technologies. Market demand is likely to drive further innovation in this area.

Upfront investment of time – know your EHR

Overall, it is advisable that the plastic surgeon, office manager, and key staff members take the time to understand the capabilities of the EHR and consider how it can best be used to

limit manual entry and increase efficiency and flow with automatic templates, linked fields, and automated alerts and tasks. Taking the time to familiarize oneself with the features of the program and configuring the system to allow the office to take full advantage of the software will encourage further efficiencies and decrease frustration in the long term. Physicians should expect to take time off (both physician and staff) for appropriate training and implementation, and should expect decreased productivity for many months, possibly years. Interestingly, though, some studies have shown that despite the frequent reduction in clinical volume that many practices encounter even years after EHR implementation, revenues have increased, presumably due to better capture of revenue with more accurate billing and coding, and more efficient workflows on the practice management side.

Photo system

Most plastic surgeons will find the photo systems offered by their EHRs to be inadequate, as they cater to primary care and other physician specialties. Accordingly, plastic surgeons may find it better to purchase or subscribe to a dedicated photo management program that links with the EHR.^{11,42} Ideally, the system should allow direct uploading from the tablet device, camera or smartphone without needing to first download to a hard drive or needing to upload and assign to correct patients at the end of the day. Categorizing photos with metatags for demographics, surgeon, facility, diagnosis, procedure(s), and other considerations like implant size and position can provide important context for building dynamic galleries without having to duplicate photos. The process for assigning tags to the image should not be laborious and tags should be easily searchable. Certain tags such as photo date and patient demographics should be automated, especially if linked to the EHR. In such a system, it would be feasible, for example, to search for all 6-month postoperative pictures of a female breast reduction patient between the age of 28 and 40 years old who had at least 600 g of reduction. Some photo systems also allow the physician to immediately annotate the image and save the annotated image as a separate (“flat-tened”) file. This is an effective patient education and risk management tool as well. When a patient can see her asymmetries or other issues visually marked or the proposed procedure illustrated (especially when done in real time by the surgeon on a tablet and broadcast to a large screen in the examination room, creating an immersive educational experience), it may increase her understanding of the limitations while simultaneously increasing her comfort with the procedure. The manner in which the photos are presented to the patient is also important. Ideally, the program should permit before and after images to be shown side-by-side and saved as such and printed with a specified number of images per page. Access to the patient's images should be enabled via a laptop or desktop computer, tablet device, or smartphone. Some programs¹¹ allow the physician to give patients access to some or all of their images via a patient portal, and others allow patients to upload their own images to their account as well. This shared access may encourage happy patients to share their experiences with prospective patients.

When transferring the photos for use on a website or PowerPoint presentation, authorized individuals with access to the photos must be vigilant that proper consent has been

obtained from the patient for online use, and that identifying information has been removed. This includes the metadata tags assigned to the photo (such as patient name, gender, date of birth, procedure, date, etc.) which may remain associated with the photo and “readable” to a web search engine like Google. Consequently, if a plastic surgeon is unaware that this metadata must be removed from the photo, a well-meaning friend of a patient may Google her friend’s name only to be directed to a set of images in a plastic surgeon’s online breast augmentation gallery. If identifying features like tattoos are easily recognized, this can add to the risk of privacy violations. Similarly, some of this same information can sometimes be viewed inadvertently when the mouse is rolled over the image. These incidents may not only lead to loss of business from disgruntled patients but may lead to charges of HIPAA violations or other legal and financial liabilities.

As is true with the EHR, it is equally important with a vendor of photo management systems to delineate in the contract who owns the data/images, who bears the responsibilities for maintenance and what are the conditions for and obligations following termination of the contract (see discussion in Contracting considerations section, above).

Practice management

Integrated single-vendor software products may include components for practice management, scheduling, billing, clinical documentation, and follow-up marketing. An increasing emphasis on interoperability of healthcare information systems provides practices with more choices and the ability to bring together digital tools from a variety of vendors. While there is often much discussion by physicians about the documentation and note-generating aspects of an EHR, perhaps more important to the overall health of the office is the practice management system used. Traditionally, practice management systems focused mainly on the billing and coding process and tracking accounts receivable. However, sophisticated modern practice management systems can streamline workflows and reporting and increase revenue capture while potentially reducing costs.

Billing

Even in the traditional arena of billing, some newer practice management programs will automatically check patient eligibility information, including verifying that the patient’s insurance is still active, identifying the amount of the deductible and how much has been met, listing benefits for in- and out-of-network visits and for inpatient and outpatient procedures, cataloging copays for studies and labs, and furnishing formularies and benefits explanations for prescription medications. This information may facilitate the collection of appropriate copays and deductibles at the time of the visit or more accurate decision-making regarding procedures and orders. Some systems have an E/M (Evaluation and Management) calculator which helps the clinician code the appropriate billing level for the office visit based on the information gathered in the progress note. For example, a sophisticated EHR using a structured data model can use Medicare E/M coding guidelines to determine the number of history, physical examination and review of systems bullets that have been satisfactorily documented, as well as provide the physician a way to override the automated

coding and bill based on time and complexity of the encounter. Many EHRs provide tools to assist in selection of the appropriate CPT and ICD codes, and may even automate the process based on anatomic and clinical data entered in the course of the progress note’s creation. After the claim is generated, most systems have a process called claims “scrubbing”, in which the claims are checked for errors prior to submission. When available, the claim can be sent either directly to a third-party payor or more commonly to a billing clearinghouse, which then sends the claims to the appropriate third party. Ideally, the interfacing of the practice management program with the clearinghouse will automatically send secondary claims to the supplemental insurance payors, where applicable, and even generate paper statements to patients as needed for billing the patient’s out-of-pocket component. Automation of this process reduces the dependency of a practice’s revenue on the caliber and dedication of personnel in the office, and when set up appropriately, reduces the frequency of missed or denied claims.

Reports

Popular practice management systems also allow access to customizable reports that help the practice track outstanding unpaid claims, revenues per facility, revenues per claim, revenues per employee, volume by procedure, etc. Historically, many such reports were difficult to obtain and were rarely generated in real time. With more sophisticated systems, practice managers and physicians can assess the viability and efficiency of their practice on demand.

Theft prevention

Practice management programs may also help decrease the risk of theft, embezzlement and similar issues by allowing books to be “hard-closed” at the end of each day. When the hard close is performed, monetary amounts and transactions can no longer be added, removed, or altered. Additionally, robust inventory management systems help track how many products have been sold, by whom, and how many products should remain in inventory, helping to mitigate against “lost” inventory, to prompt timely restocking, and to facilitate more accurate tracking of revenue generation from the sale of each unique product stock-keeping unit (SKU).

Customer relation management

Newer systems also feature customer relation management (CRM) modules for tracking leads, following patients for recurrent revenue opportunity, and engaging patients with appropriate marketing materials. Some of the common features of CRM products include the ability to send targeted timely emails or letters based on patient demographics, procedure types, time elapsed from prior appointment dates, etc. Properly used, CRM can be deployed even before the patient comes into the practice. The system can start engaging the patient the moment an inquiry is made on a website, a subscription to the practice’s electronic newsletter is enrolled, or a patient appointment call is made. When these inbound communications are received from prospective patients, automated customized emails or letters can be sent prepopulated with appropriate information and on a predetermined schedule. For example, in the case of a new breast

enhancement patient, the process may be set up as follows: an initial welcome message is sent after the patient has scheduled an appointment, an appointment reminder is delivered via SMS or email one week after inquiry and again 3 days before the scheduled appointment (with a request for the patient to acknowledge receipt and confirm the appointment time with a quick text or reply which is automatically registered in the system), a “thank you for coming” message with a succinct visit summary is delivered the day after the patient is seen, a follow-up message is issued asking if the patient desires more information if an appointment for surgery has not been scheduled within 4 weeks, and so on until after the surgery is completed. Reminders for postoperative appointments, due dates for neurotoxin and filler treatments, special promotions and events can all be delivered and tracked with sophisticated CRM tools.

On-site patient education

Using digital technology for patient education can enhance patient comprehension of complex medical information, and modern devices and software products can make this a highly interactive experience. When used effectively, such technology can increase the patient’s confidence not only in the treatments selected, but also in the surgeon whose competence may be reflected in the selection of state-of-the-art modern tools used in the office.

Digital educational materials

The office encounter may be enhanced by interactive informational videos or materials that patients can be viewing in the reception area or in the examination room as they are waiting to see the physician (Fig. 36.3). These may include slide presentations, animations, video tutorials and other media, and may be professionally developed, licensed from third parties, or generated in-house by the physician’s practice. Digital information on other available procedures and products may open the door to further discussion on a topic or procedure about which the patient was previously unaware. As stated previously, during the encounter the real-time use of photographs and illustrations that can be annotated may help the surgeon explain the procedure in detail or show asymmetries and other considerations that are specific to the patient.¹¹ More elaborate programs allow the annotated images to also be saved seamlessly to the patient’s chart. Some tablet EHR products also boast highly detailed virtual anatomic atlases featuring multiple touch-sensitive zones, allowing explanation of pertinent anatomy and techniques with multiple views and layers (Fig. 36.4). The initial consultation is often a prime opportunity for plastic surgeons to showcase their artistic skills with quick sketches of procedural steps, incision locations, etc., drawn before the patient’s eyes in real time.

Digital simulation

Digital simulators may also allow the surgeon to better demonstrate to the patient and companions the possible outcomes of a procedure, and may also assist in surgical planning. Most of these are stand-alone systems that in some cases can be linked to the practice’s EHR. Some require special hardware and a dedicated area of the office designated as an image

capture room.⁴³ Other systems⁴⁴ only require an iPad, camera phone, or regular camera to capture three traditional-position images (frontal, right lateral and left lateral) in any room (Fig. 36.5). With sophisticated computer algorithms, the photos are interpolated into a three-dimensional image that can then be manipulated in the software. The same system also allows three-dimensional scanning with a commercially available sensor attachment for the iPad (Fig. 36.6). The resultant image can then be manipulated to help the patient visualize possible outcomes and provide useful feedback about specific aesthetic goals (Fig. 36.7). For breast augmentation planning, virtual breast implants selected from a menu categorized by manufacturer, size, shape, and dimensions may be added and different implant choices may be viewed side-by-side. With multiple views and what-if scenarios, the patient can assess differences in projection, shape and width. For example, three-dimensional modeling can help the patient better understand the difference between a shaped or round implant and help her to decide whether the projected result is worth the added expense. For a patient seeking breast reduction, digital simulation may help to show the patient a representative image of what a reduction of 500 g of breast volume (as may be required by her particular insurance) would look like, to help her decide if she would like to commit to insurance coverage, or instead pay out-of-pocket for a more limited breast reduction that preserves more volume. The program allows for differential subtraction of volume on each side which can be helpful in planning secondary breast revision cases and post-mastectomy reconstruction. In the evaluation of the mastectomy patient for post-mastectomy reconstruction, this feature may permit the surgeon to subtract the entire volume of the breast and then place a variety of virtual implants to assess the best direct-to-implant choices for the patient. When counseling candidates for augmentation mastopexy, who often have difficulty understanding the necessity of both components in their surgical plan, the simulation helps to illustrate what the breast may look like with an implant alone without the mastopexy and vice versa. With facial and body images, the programs allow the surgeon to simulate various procedures including reshaping, retexturing, and filling with a variety of topical treatments, injectable products, laser and energy devices, liposuction systems, etc. The surgeon can also model widening/narrowing, advancing/recessing, and raising/lowering of various structures such as the chin, brows, nose, eyes, cheeks, etc. One vendor’s software fabricates full facial replicas with 3D-printing technology, and integrates with some 3D camera systems used for other clinical simulation tasks to create an even more comprehensive visual and tactile representation of the patient’s features for more detailed modeling.⁴⁵

Some programs allow the patient to upload pictures securely from home to the physician’s website (Fig. 36.8). The photos are incorporated into simulation software, and patients are then encouraged to schedule an office visit to see these simulations and discuss treatment options with the surgeon. In so doing, these tools move beyond education and may serve as a means of differentiating the surgeon in the market and recruiting prospective patients. Finally, some programs allow patients secure online access to a portion or all of their images remotely, as determined by the physician, and some offer easy social media sharing options. Thus, happy patients may share their results with friends (Fig. 36.9).

⬅️ Brow Lift

Brow Lift Risks



Brow Lift Risks:

Each year thousands of women and men undergo successful brow lift procedures, experience no major problems and are happy with the results. Significant complications from a brow lift are infrequent. However, make sure you understand what surgery involves, including possible risks, complications and follow-up care.

A brow lift poses various risks, including:

- Excess scarring.
- Facial asymmetry.
- Temporary or permanent hair loss near the incision.
- An accumulation of blood under the skin (hematoma).
- Changes in skin sensation in your brow and/or forehead area for a few months up to two years.
- Forehead nerve damage which can result in loss of the ability to feel or raise eyebrow and/or forehead area.

- The need for revision surgery to correct rare complications of the brow lift surgery.

Like any major surgery, a brow lift poses a risk of bleeding, infection and an adverse reaction to anesthesia. It's also possible to have an allergic reaction to the surgical tape or other materials used during or after the procedure.

You can help minimize certain risks by following the advice and instructions of your surgeon, both before and after your brow lift surgery. If you have any concerns about the risks involved with a brow lift surgery, please consult your surgeon.

Brow Lift Illustrations



Rela

Rhinc

Facel

Eyelid

Perm

(A)

⬅️ Rhinoplasty

Rhinoplasty Overview



About Rhinoplasty:

Rhinoplasty, also known as nose surgery, is a common procedure to improve the appearance and proportion of the nose. It can also be performed to correct birth defects, breathing difficulties, or to repair deformities caused by injury. Changing the size, shape, or proportions of the nose can often help improve self-confidence.

Rhinoplasty Considerations



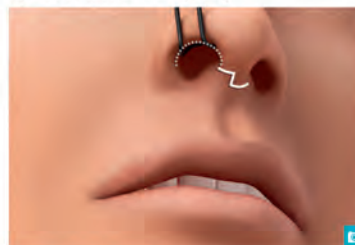
Rhinoplasty Considerations:

The best candidates for rhinoplasty have realistic expectations and are interested in improving the appearance and/or function of the nose. Before you decide to have rhinoplasty carefully think about your expectations and discuss them with your surgeon. The following conditions could indicate that rhinoplasty surgery is right for you:

- Nose is not in proportion to the rest of the face.
- Nasal tip is drooping, upturned, hooked, or enlarged.
- Nose bridge has humps or depressions.
- Nostrils are too large or wide.
- A history of nasal obstructions or breathing problems.

Rhinoplasty is often postponed on younger patients until the nose has completed its growth, typically around 15 or 16 years of age.

Open vs. Closed Rhinoplasty



The closed rhinoplasty approach uses surgical incisions inside the nostrils, avoiding a visible scar. This approach may reduce swelling time. However, this approach limits access to the internal structure of the nose, so more complex rhinoplasty procedures may require the open approach.

The approach you choose greatly affects the results. Your surgeon will help you choose the approach they feel is most appropriate for your goals and the results you desire.

Open vs. Closed Rhinoplasty:

There are two different techniques, or surgical approaches, used for rhinoplasty. These include open and closed rhinoplasty. Patients considering nose surgery should be aware of the differences.

The open rhinoplasty approach, also called external rhinoplasty, uses a few hidden incisions made inside the nostrils and adds a small bridging incision, called a trans-columellar incision, to connect the right and left nostril incisions. With the addition of this tiny visible incision, the nasal skin can be folded upward (much like opening the hood of a car) giving the surgeon more access to the internal structures of the nose. This allows for more precision and ease while sculpting the nose. When properly performed, the open rhinoplasty incision heals remarkably well and becomes nearly invisible.

(B)

Fig. 36.3 Interactive brow lift (A) and rhinoplasty (B) informational screens with access to videos, illustrations and other educational content. (© 2015 TouchMD, an ALPHAEON Company. Used with permission. All Rights Reserved.)

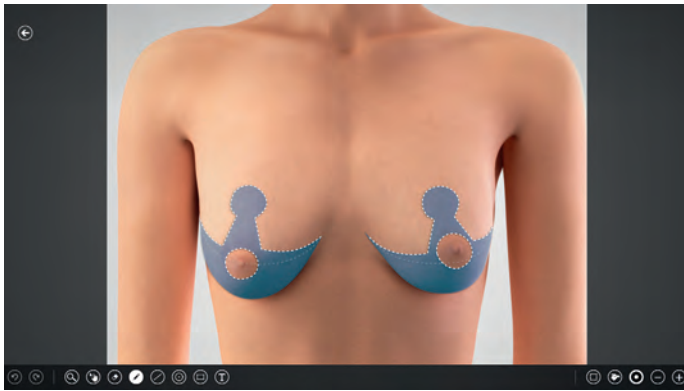


Fig. 36.4 Illustrations that can be annotated and saved for the patient to access later via their portal can be an effective patient education tool. (© 2015 TouchMD, an ALPHAEON Company. Used with permission. All Rights Reserved.)

However, consideration should be given to whether the simulated image can be misconstrued as an implication of a guaranteed result – all images and all sessions should emphasize that the images are not a guarantee and are estimates only to be used for educational purposes. Printing a disclaimer to this effect on any image that the patient is able to view outside the office or which goes into the medical record may serve an important role in setting expectations and documenting the limitations of digital simulation tools.

On-site clinical information and decision-making

Digital technology may also assist the surgeon in clinical information and decision-making. As mentioned in the previous section, digital simulation is not only a patient education tool but can be used to help patients and surgeons plan and choose appropriate techniques, breast implants or other procedural components at the time of the office encounter.

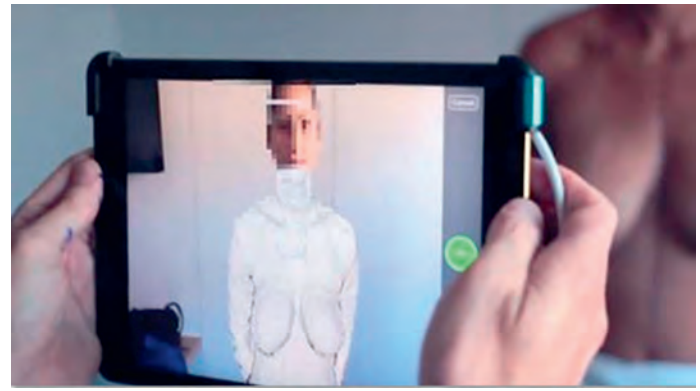


Fig. 36.6 Image processing systems may also allow for images to be captured with the Structure sensor scanner on an iPad, creating instantaneous reconstruction. (Image courtesy of Crisalix.)

Digital technology may also allow access to a specific specialist consultation from a remote location. This may be in the form of an intra-specialty or inter-specialty consultation. With newer products that are HIPAA-compliant and with the use of high definition video camera systems, the remote consultant can see and hear the interaction and advise in real time during the patient encounter. This may bring needed expertise to aid in the care of patients in a remote or underserved region with limited services or may facilitate additional expert opinion for complex cases. Military battlefield triage and surgical stabilization may be aided by similar telesurgery technologies.

Digital tools have also granted easier access to services during a visit that were previously unavailable. For example, translation services are available via a smartphone app⁴⁴ where the patient's language is selected, a translator calls the phone and provides translation for the entire interaction from a remote location. This is also available for patients requiring sign language interpretation via an online platform,

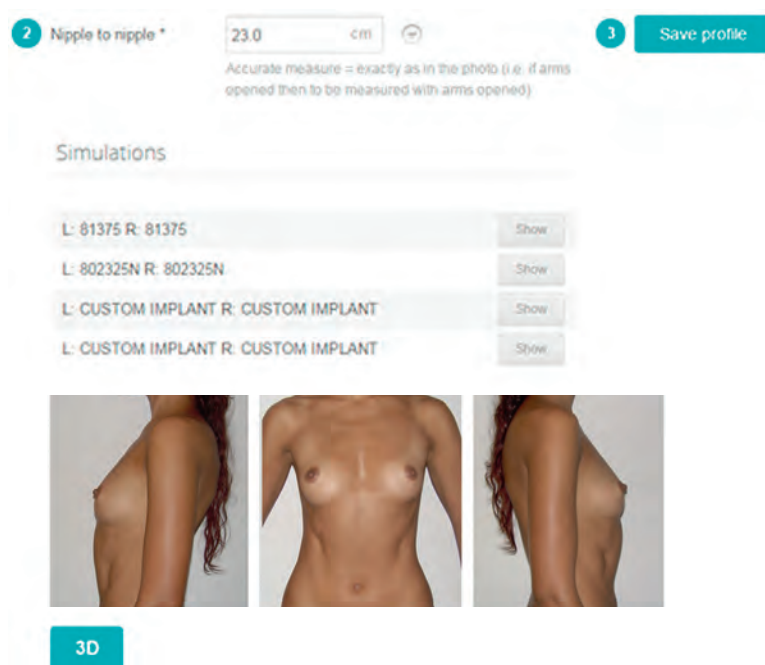


Fig. 36.5 Some systems allow images to be captured either with a traditional camera or mobile device in three views and uploaded for automatic 3D reconstruction. (Image courtesy of Crisalix.)

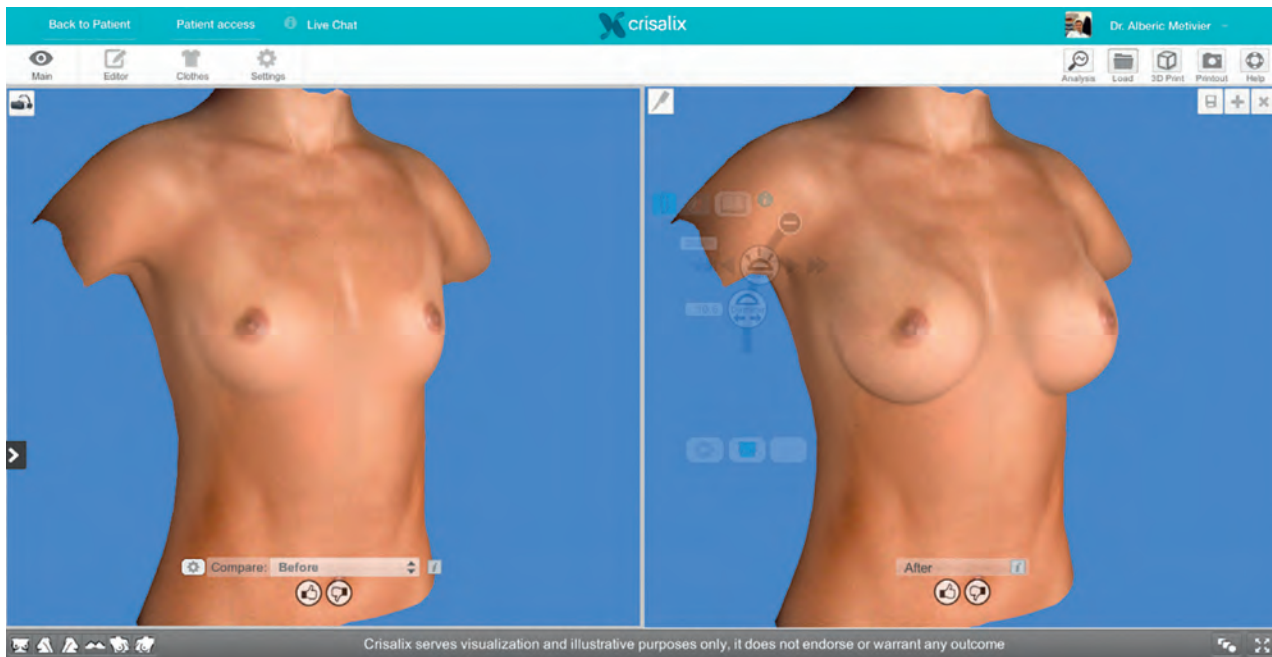


Fig. 36.7 A 3D reconstruction of the breasts can be manipulated to choose different implant brands, size, shape, texture, pocket position. Options for mastopexy and implant/volume subtraction also exist. Sample before and after view. (Image courtesy of Crisalix.)

increasing accessibility and decreasing the cost to the office of hiring an in-person sign-language interpreter for compliance with the American Disabilities Act (ADA).^{46,47}

Perioperative digital technology

Digital technology is increasingly playing a role in the preoperative, intraoperative and postoperative phases of patient care. Following initial consultation and establishment of a patient's candidacy for surgery, a number of digital tools, including devices and software systems, are available to properly plan, execute, and immediately monitor patients after complex procedures. As capabilities advance and processor

speed, chip memory, cloud storage infrastructure, and mobile/wireless technologies evolve, a fully integrated operative suite with a system of interconnected devices and programs is not only feasible, but may become the norm in the near term.

Preoperative work-up

Assessing photographs in preoperative planning

The preoperative workup for a patient often begins during, or shortly after, the initial consultation. Properly captured patient history and physical information in an electronic medical record can be reviewed along with digital photographs that are marked to the patient's chart. As described in



Fig. 36.8 Some programs allow the patient to upload pictures securely from home. The patient is then encouraged to schedule an office visit in order to see the simulations and discuss treatment options. (Image courtesy of Crisalix.)



Fig. 36.9 Some systems offer patients remote online access to designated reconstruction images with social media sharing options. (Images courtesy of Crisalix.)

the Photo system section above, sophisticated EHR tools and photography archiving systems allow for categorizations of patient photos with metadata tagging for properties like procedure type, date of procedure, diagnosis, body location, patient age, gender, insurance type, place of service, operative phase (pre-, intra-, or postoperative), etc. A dynamic registry that contextualizes the patient's photographs can allow the surgeon to view a patient's preoperative photos among those of other patients with similar demographic, anatomic or other characteristics, to build a tailored operative plan. For example, the surgeon planning a rhinoplasty on a 30-year-old African-American patient may label her photographs with tags like "dorsal hump reduction", "African-American", "30-35", "open tip", etc. The surgeon could compare this index patient's photos to those of other patients whose photos were similarly tagged. The surgeon's pictorial record database becomes richer and more easily mined for the kinds of photos needed in any given context by being able to filter and sort through images based on these kinds of tags. Some standalone applications⁴⁸ provide such searchable metatagging and cataloguing of photo galleries on tablet devices (Fig. 36.10).

Digital simulation in preoperative and intraoperative planning

Additionally, photography archiving software programs equipped with morphing and annotation tools allow the

surgeon to non-destructively mark up a set of preoperative photographic images to incorporate preoperative planning ideas. This is commonly performed in rhinoplasty and breast surgery, where unmarked and marked reference photographs obtained prior to the onset of swelling and other intraoperative changes can serve as a continuous guideline throughout the conduct of an operation. It is particularly useful to have the ability to tag photographs with appropriate metadata asynchronously to the patient visit, so that additional pertinent information can be annotated to an image set even after the patient has left the office. Accessing photographic records remotely via cloud-based systems or virtual private networks (VPNs) allows the surgeon to be reminded of the surgical plan, to add information that may be generated after contacts with the patient, and to print or view photos when delivering care at a remote point of service (for example, when performing surgery at a hospital using a different, on-site record system).

Preoperative quotes and informed consent

Estimating financial responsibility for patients for aesthetic and reconstructive procedures is an equally integral part of plastic surgery office workflow, and the process of obtaining informed consent is, of course, critical to proper patient care, serving as a safeguard for proper procedure selection and as a legal record of the information provided to the patient.

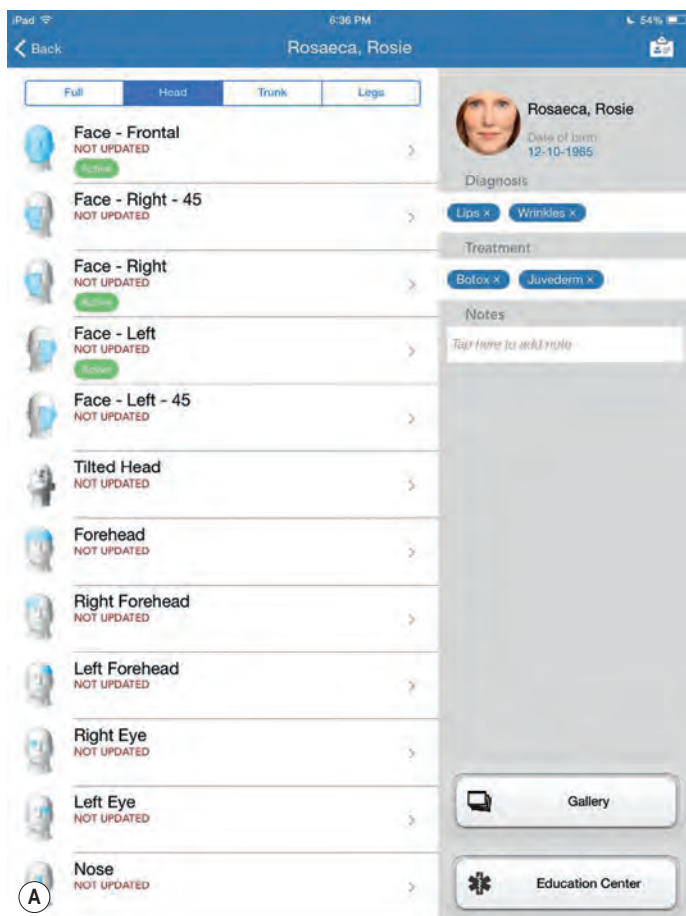


Fig. 36.10 MyAppwRx.com images. (© 2015 AppwRx, used with permission. All rights reserved.)

Many EHR systems incorporate consent and quoting modules that automatically populate from information documented into the EHR from the clinical encounter, in some cases generating ICD-9 and ICD-10 codes, CPTs and fee schedules automatically. One of the earliest programs with this functionality was a client-server software program that created custom surgical quotes and informed consent booklets prepared for a specific patient based on procedures proposed and selected by the surgeon or appropriate office staff for populating the document outputs.⁴⁹ Many new software tools allow the patient to be sent quotes and consent forms via privacy-protected portals (often the same portals created for the patients to access pre-consultation educational materials and intake forms), so they may be reviewed by the patient, shared by the patient with family or caretakers, and, in some cases, completed. HIPAA-compliant online systems like DocuSign may be used to capture electronic signatures if deemed appropriate by the surgeon. The American Society of Plastic Surgeons (ASPS) informed consent library is available in CD and digital download format for surgeons to print and use in the office; some EHR systems allow pre-existing forms to be converted into smart PDF or other formats that allow signatures to be captured in the EHR application as well. Alternatively, other EHRs facilitate copy-and-paste functionality that allows the content of other consent forms to be “digitized” into the EHR’s library of forms.

Preoperative labs and studies

In addition to surgical quotes and consent tools, preoperative planning includes the ordering and reviewing of laboratory, radiographic, or other clinical data, as well as provision of prescriptions for perioperative medications. Most EHR systems in the United States are equipped with capabilities for electronic prescribing through Surescripts or similar platforms which connect to most pharmacies, reducing the requirement for generation, signing, scanning and faxing of paper prescriptions. Similarly, electronic computer provider order entry for laboratory and radiographic studies is built into many EHR programs. In many cases, these provide a means for the direct electronic transmission of orders to laboratory centers like Quest and LabCorp as well as for the receipt and filing of the results into the patient’s record. This automation holds some promise for accelerating the process of ordering and reviewing labs for the surgeon and office staff, and, where available, can be applied both preoperatively and postoperatively. Radiographic images viewable in PACS systems can sometimes be directly incorporated into the medical record along with the radiologist’s reports.

Automated preoperative workflows

The wide array of integrations between healthcare information technologies, often employing the Health Level 7 (HL7) language of data transmission, holds promise for additional methods of automating workflows.⁵⁰ Already, many practice management (PM) systems are integrated with the EHR programs of other vendors, allowing a “mix-and-match” approach to selecting office software solutions. Some vendors offer all-in-one solutions with EHR, PM, inventory and other features with internal integrations allowing automatic transfer of data such as diagnosis, date of service, procedure codes,

surgeon and patient information, etc., between the component modules. In some cases, this allows customized “workflow ladders” of task assignment and accountability chains to be configured in the software, where specific tasks involved in a preoperative or postoperative protocol for a patient can be assigned to individual staff members and the “baton” handed between them as steps in the protocol are completed. Well-integrated systems also allow these steps to be documented into the EHR, memorializing the date, time, responsible staff member and any notes pertinent to the workflow. As mobile technologies mature further, secure messaging and task recording on mobile devices help facilitate truly paperless office workflows.

Preoperative risk assessments and tools

In some cases, automation can also be applied to algorithms for preoperative risk assessment and management. For example, data entry tools in EHR programs can permit calculation of a Caprini DVT risk score, along with peer-reviewed evidence-based recommendations for appropriate prophylaxis. Calculation of ASA score, Fitzpatrick Scale, and other metrics is feasible with protocols coded into software for the perioperative patient evaluation. Some EHR vendors provide customization tools that allow practices to digitize their existing forms for such purposes, often working in tandem with the surgeon and staff in a collaborative development process. Such systems can help surgeons and facilities maintain compliance with documents required by AAAASF (American Association for Accreditation of Ambulatory Surgery Facilities) and other accreditation bodies, by permitting digitization of the necessary surgical checklists and other forms.

Preoperative modeling

Patients requiring more elaborate preoperative workups for craniofacial, microsurgical or other complex procedures can also benefit from digital technologies. While its necessity is not clear in all cases, digital angiography is commonly utilized as part of the preoperative assessment of patients undergoing perforator flap reconstruction and other microsurgical procedures. With the advent and increasing popularity of 3D printing, custom mouldages and cranial prosthesis for complex, composite craniofacial reconstructions for trauma, oncology, or craniosynostosis can be architected, utilizing 3D reconstructions of CT, MRI and other radiographic data along with digital photography to model the multi-dimensional topography of the patient’s current or anticipated defect. Sophisticated CAD/CAM tools^{51–53} can be used to create the anatomic models from which implantable constructs of titanium, methylmethacrylate (MMA), acrylics, hydroxyapatite (HA), bioceramics, polyetheretherketone (PEEK), and other materials can be machine-fabricated. Whole structure implants such as custom mandibular titanium plates may also be designed and manufactured. Composites of biologic and inert substances incorporating dermal matrices, stem cells, bone graft, chondrocyte scaffolds and other materials can also be designed and modeled. The availability of custom tissue engineering products from companies like Organovo and relatively inexpensive consumer-focused 3D-printing devices like the MakerBot holds promise for considerable ongoing innovation in preoperative design and prototyping for complex procedures.

Day of operation

Immediate preoperative digital technology

Once the patient has arrived for surgery, a number of tools are available for the immediate preoperative assessment. Many bedside digital vital sign monitors now include Bluetooth connectivity as well as integration directly into EHRs. Additionally, remote home vital sign monitoring is available from a variety of application vendors, with biometric parameters tracked by tools like HealthKit from Apple or Google Fit. Certain EHRs can pull forward medical history contained in prior clinical notes for the surgeon, anesthesiologist or other providers to review in the preoperative holding area. Immediate preoperative patient education can be enhanced similar to the initial office consultation, with streaming video content available through Apple TV, Google TV, and other wireless devices broadcast to video screens in private holding rooms. Preoperative checklists for the operating room staff can be put into clinical workflows in the EHR with electronic signing and attestation available for the appropriate staff members.

Intraoperative monitoring

The operating room is another venue for integration of digital technology in the care of the plastic surgery patient. Digital anesthesia monitoring is available in many operating rooms, although direct integration of the data into EHRs remains a challenge for many vendors. Often, this continuously acquired, streaming data is condensed into photographic summaries which serve the purposes of documentation but may be limiting in terms of data analysis capabilities. More direct integration of data from these systems into EHRs is anticipated and promoted by the FDA, Center for Medical Integration and other organizations, consistent with the HITECH Act's goal of promoting interoperability.⁵⁴ Other digital innovations may further improve patient safety; for example, radio-frequency identification (RFID) technology is being used to monitor lap sponges in the operating room. Companies are currently working on the concept of data fusion, which integrates various inputs such as imaging modalities and software algorithms that allow a hybrid 3D output, for example, or an integrated display of all relevant clinical information that could be real-time, streamed on mobile platforms, and potentially allowing for the superimposing of data and other image on a surgeon's visual field, either through a screen monitor or a wearable platform for real-time feedback/imaging during a procedure.⁵⁵

Intraoperative communication and collaboration

The surgeon in the operating room can also take advantage of certain digital technologies where appropriate. Digital point-of-view (POV) camera devices like the GoPro camera⁵⁶ and Google Glass can facilitate education of students and residents in the OR or at remote sites, providing the surgeon's vantage point to interested observers, allowing recording of surgical procedures for educational, marketing or quality assurance purposes, and providing a clearer picture of hard-to-see small spaces, like the nasal vault during rhinoplasty. Some surgeons utilize such technologies to engage in additional hands-free communication as necessary with staff and other parties outside the operating room. Telesurgery in

combat field hospitals, developing countries, rural locations, and other points of service may be facilitated through these POV technologies, which permit a remote surgeon to provide guidance and instruction to treating providers on site, possibly providing improved patient stabilization, triage, and second opinion consultation. Already there have been numerous publicly reported examples of surgeons utilizing Google Glass in surgery, including augmented reality overlays of surgical illustrations and procedural steps that are superimposable upon the patient's anatomy to help guide the conduct of a procedure.^{57–59}

Intraoperative tools for surgical decision-making

Surgeons working closely with pathologists on intraoperative pathology reporting may have access to sophisticated integrated digital pathology solutions incorporating smart digital scanning, image processing, archiving and analysis.⁶⁰ The surgeon engaged in microsurgery may utilize operating microscopes equipped with digital optics and video recording systems, and implant digitally monitored implantable Doppler probes to assess anastomotic patency. Tissue perfusion quality may be ascertained with the use of technology allowing intraoperative decision-making for debridement of tissue at risk for necrosis or interrogation of threatened vascular pedicles.⁶¹

Postoperative digital technologies

As a surgical procedure nears completion, continuation of perioperative workflow checklists can resume in the EHR. Geolocation systems employing protocols like global positioning system (GPS), radio-frequency identification (RFID), near-field communication (NFC), Bluetooth, wi-fi, internet protocol (IP), and uplink-time difference of arrival (U-TDA) cellular technology, can potentially track the whereabouts of the patient and staff members for accurate recording of surgical times, allocation of beds and human resources, and other location-based services. The intraoperatively placed Doppler probes can provide ongoing postoperative flap monitoring, and vital sign applications can stream continuous physiologic data to the physician's smartphone. Numerous additional uses of digital technologies can be envisioned and designed by innovative plastic surgeons in collaboration with engineers, software developers, and other clinical providers.

Digital technology between patient visits (including long-term follow-up)

Introduction

With advanced practice management/customer relationship management programs, monitoring with wearable technology and accessories, and online and other digital forms of patient and community engagement, physicians will be able to track and customize their engagement with their patients and community throughout their lifetime.

Direct patient communication

Communication in the form of HIPAA-compliant apps⁶² is already possible and widely available. The technology allows

for real-time, video, chat, and picture-sharing capabilities, as with the virtual consultations discussed previously.

Surgeons wishing to discard pagers and arcane answering systems may still provide round-the-clock phone contact accessibility to patients, hospitals and emergency rooms using free services such as Google Voice. The service can be set up such that, when the patient calls the plastic surgeon's Google Voice number, it will ring any combination of land lines, mobile numbers, desktop computers, etc., simultaneously. The phone call can be screened, answered, or sent to a cloud-based voicemail. Voicemails can be transcribed and emailed and/or texted to the plastic surgeons. Alerts can be set to ring with different tones and set to different answering messages depending on the number calling. In addition, the plastic surgeon can use Google Voice to return the call to the patient without revealing their home phone or mobile number. The plastic surgeon may also choose any area code for their Google Voice number. To the patient, the Google Voice number is like any other number. Google Voice also allows free landline and mobile number calls to the entire US, Canada and Mexico. Of course, it may be necessary to have a back-up system such as a very basic answering service plan, to mitigate in the event of natural disaster, or other possible disruptions to the surgeon's access.

Other postoperative patient engagement tools are designed specifically to track adherence to postoperative care protocols and field inquiries from patients during their recovery. In addition to the telemedicine applications described above, plastic surgery offices can take advantage of mobile applications with secure messaging, patient compliance questionnaires, and private photo sharing. The patient or caretaker can send photos of healing incisions or body locations of concern for a quick triage regarding the urgency of follow-up.

Enhanced postoperative recovery protocols that include step-by-step guidance for recovery (e.g., "Walk 10 steps every 3 hours on postoperative day one; advance from a clear liquid diet to a low salt diet on postoperative day 2, etc.") can be built into checklists or messaging sequences with automated callbacks and alerts when patients are not responding affirmatively to requirements.⁶²⁻⁶⁶

Patient monitoring with wearables and accessories

Follow-up after the immediate postoperative period may sometimes be achieved with virtual visits and wearable or portable technology for monitoring. Current technology already enables EKG tracings, noninvasive blood sugar monitoring, heart rate, and dermoscope readings at the hands of the patient. Portable ultrasounds and heart rate monitors, and pulse oximeters are also available as attachments to smartphones.

There is great potential for innovation in the field of patient wearables for monitoring. For example, in the area of wound care, one project is developing wearables that include multiple sensors to detect pressure, monitor for infection, and adjust negative pressure applied to chronic wounds.⁶⁷ Newer products⁶⁸ can provide real-time feedback on plantar foot pressure to aid in the prevention of ulcers in diabetics and patients with other forms of neuropathy. One company⁶⁹ offers a wearable device that provides gait, balance and other postural analysis to assist in physical rehabilitation. Numerous consumer health

wearables have gained popularity in recent years, including the Jawbone UP systems for portable heart monitoring, Fitbit activity trackers, and the Apple Watch. Third-party apps can integrate physiologic, nutritional and other activity data from multiple devices and wearables into single portals where patients can confer with caregivers and advisors to craft personalized wellness plans. Future advances might include sensors incorporated into implants, wound dressings, or directly into tissue. These could offer feedback and remote monitoring of the wearer of the implant, status of the wound, infection, malignancy, etc., with the capability to transmit the information for remote access via a mobile app or a physician portal. The use of long-term monitoring and patient engagement between encounters is still in its infancy in terms of technology and adoption, but the potential of a major paradigm shift in healthcare delivery appears promising.

Patient community engagement online

Postoperative patient care, much like patient lead generation, has been impacted by the popularization of social media, with patients regularly sharing results, testimonials and detailed descriptions of their patient care experiences through a variety of media vehicles, including Facebook, Twitter, Instagram, Snapchat, blogs, and other interactive forums. Newer "crowdsourcing" sites for discussion of practice paradigms and medical advice sharing have proliferated, affording a venue for dynamic discussions between patients and other patients or between patients and providers. Engaging in such forums requires the surgeon and office staff to be ever mindful of HIPAA and other privacy considerations, but nonetheless can provide important education for patients recovering from procedures. One of the more popular and heavily trafficked crowdsourcing sites for medical recommendations and advice in the aesthetic plastic surgery field⁷ entails many surgeons responding regularly to inquiries from prospective patients as well as those who have undergone procedures by other providers. Many surgeons actively curate their profiles and activities on that and other sites as part of a general social media and marketing strategy; a number of additional crowd-advice sites have steadily gained in popularity.^{14,70} Patient-centric forums⁷¹ that focus on specific disease experiences have also given patients as consumers of healthcare an important role in patient referral patterns, treatment evaluations, and clinical trial design. The digitally empowered patient can have an important influence on a surgeon's reputation, search engine optimization, and word-of-mouth marketing success via online review sites.³⁻⁷

Digital technology in plastic surgery education and training

Perhaps nowhere is there more promise for impactful utilization of digital technology than in the arena of medical education and training. A new era in training capabilities has dawned with the advent and popularization of highly sophisticated virtual and augmented reality simulators. The Oculus Rift^{72,73} and other⁷⁴ systems have both shown great promise for creating highly immersive, multi-sensorial experiences incorporating photorealistic 360° video environments, accompanying audio and, perhaps when combined with wearable sensors,

tactile feedback. The conceivable applications of such technologies for simulation of surgical procedures, resident skills assessments with feedback looping, microsurgical training replete with tremor reduction and highly detailed magnification, and other applications are myriad. Similar to the intraoperative applications of augmented reality cited above, other vendors⁷⁵⁻⁷⁷ are exploring methods to incorporate CT and other radiographic data into simulations, in combination with instrumentation that provides verisimilitude to the tactile experience of handling real tissues. While not a substitute for direct intraoperative experience, these tools could provide important adjuvant learning and preparation toolkits for students and residents, particularly in early years of training. Some institutions have begun using surgical simulation as a core component of residency training, with intraoperative feedback provided during the simulation and procedures recorded for subsequent debriefing. The intraoperative use of point-of-view (POV) technologies such as Google Glass and the GoPro camera can provide the ability to communicate from the operating room in real time with images, video and chat tools to enhance the education of residents and other surgeons. It may enhance the perspective of a resident who may or may not be physically present as another surgeon performs the procedure or, alternatively, it may augment the viewpoint of the attending surgeon who may or may not be in the same room, while the resident performs the procedure. With routine use, POV systems can help facilitate the curation of a large educational surgical video library that can be streamed remotely on demand.

These technologies, in addition to other simple HIPAA-compliant apps that allow real-time chat, video, and audio, can also enhance communication and education in the emergency department or during other consultations where a picture or video is much more effective than a verbal description. This can be extremely helpful in the appropriate triage and staging of patients with lacerations and complex wounds, some of whom can be appropriately managed in the emergency room (by emergency department staff or the plastic surgeon) while others require care in the operating room. They can also be used for assessment and education of practicing plastic surgeons who are learning either in a simulation or by evaluation of the surgeon's actual cases. Larger scale review of various surgeons' procedures could also lead to formulation of best practice guidance for operating efficiency that can enhance resident education and continuing medical education.

Even the classic anatomic atlas has experienced digital innovation: several products^{78,79} provide multilayered and multi-view anatomic images, allowing a walk-through of every layer of the human body and individual organs, holding some promise to potentially decrease the need for human cadaver-based dissection, or to provide educational resources to supplement cadaver dissections. Coursework in medical school and lecture series during residency can benefit from digitally deployed course syllabi using numerous e-learning and distribution programs, with surgical textbooks as well as articles from plastic surgery journals and assorted relevant periodicals available in electronic format for reading on iPad, Amazon Kindle, or other handheld e-readers and tablets. Continuing medical education is facilitated by online articles, quizzes, Inservice exams, and conference webinars, with participants being able to attend, rate and claim credits for certain such activities on any web browser-enabled device.

Plastic surgeons and residents interested in additional education and training in information sciences have numerous opportunities in both degree-granting and executive education certificate programs focusing on bioinformatics/medical informatics, information systems, technology-enhanced education, device and software innovation and entrepreneurship. Master's degrees in bioinformatics or information systems often may be obtained on a part-time basis, with limited time disruption on other professional obligations or clinical practice momentum. Many MBA programs, both part-time and at the Executive MBA level, offer coursework in technology innovation as well. There are also numerous industry symposia, both sponsored within the plastic surgery professional organizations and within the digital health space, focusing on technological innovation pertinent to patient engagement, medical records, photo-documentation, telemedicine and telesurgery, practice management software, concierge-level wellness coaching, device design, bench-to-market strategy, venture financing, etc. Several professional societies, including the Healthcare Information and Management Systems Society (HIMSS), the American Medical Informatics Association (AMIA), and others provide annual meetings and educational opportunities that afford physicians exposure to a wide array of vendor products and services, key opinion leaders, advocacy programs, regulatory guidelines and other offerings. Many of these symposia and meetings provide formal Continuing Medical Education credits and serve as professional networking venues. At the intersection of innovation, venture funding, and clinical applications are several organizations that provide online newsfeed content as well as sponsorship of such meetings; examples include Singularity University's Exponential Medicine conference, VentureBeat and its associated HealthBeat conference, Digital Health Summit, and many more.

Digital technology for the advancement of plastic surgery (research and clinical outcomes and advocacy)

The advent of inexpensive and highly scalable storage and processing capabilities, along with the ubiquity of handheld mobile technology and wireless communications, has opened up numerous opportunities to mine and analyze large datasets for trends and outcomes information.

Residents training in surgery, as well as board Diplomates who participate in Maintenance of Certification programs, may participate in data registries such as the Tracking Outcomes in Plastic Surgery (TOPS) and ABPS board collection modules. Other plastic surgeons are required to participate in the DataHub for accreditation of their ambulatory surgery facilities by AAAASF.⁸⁰ Clinically targeted registries such as the National Breast Implant Registry⁸¹ and the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma (ALCL) Etiology and Epidemiology (PROFILE) registry⁸² (both cooperatively developed between the Plastic Surgery Foundation and the FDA), and the General Registry of Autologous Fat Transfer (GRAFT)⁸³ have also been developed out of the recognition that real data is needed to answer important questions of safety, efficacy, and long-term outcomes.

Some EHR platforms allow case information entered into the clinical record to be directly integrated into certain registry programs, reducing the need for double data entry and providing a natural method to track case volume and complications. Surgeons participating in state public health registries and alert systems may sometimes take advantage of direct EHR data exports through the Fast Healthcare Interoperability Resources (FHIR) or Direct Protocols for health information exchange that allow automatic uploading of data transfer with other programs, registries and systems. As EHR adoption increases, it is hoped that even more seamless interfaces with automatic information transfer and portable data models will ease the administrative burden on physicians and their office staff.

Gathering of large-scale volumes of data is facilitated by improvements in automated technology. When combined with structured data architecture and natural language processing, these aggregates, often called “Big Data”, hold significant promise for assisting the evolution of healthcare from evidence-based medicine to *precision* medicine, in which data informing the likely outcomes specific to a subset of a population or an individual can be utilized to facilitate better clinical decision-making and treatment protocols. Precision medicine can be informed by clinical information furnished through medical records, healthcare claims, crowdsourcing sites,

wearable technology, patient genomics, and other sources of individualized data.

Furthermore, as reimbursements from third-party payers becoming increasingly tied to value-based compensation, and as healthcare policy-makers increasingly regulate medical practice, the access to and analysis of Big Data will help plastic surgeons and their specialty societies substantiate anecdotal evidence of efficacy, safety, cost-effectiveness and other endpoints. Prospective data may also help mitigate against unsubstantiated panic with every potential question of safety, or alternatively, may identify safety issues before they trigger a national crisis.

Crowdsourcing of clinical workflows and outcomes data may allow the physician community to converge on best practices which maximize patients’ safety, longevity and satisfaction. Digital platforms that are easily accessed, easily shared among providers, and easily analyzed may also help plastic surgeons collaborate to conserve resources, streamline workflow, decrease redundancies across practices, and improve practice efficiencies. Some physicians are utilizing technology to create virtual group practices which maintain independent practice identity and autonomy while maximizing the efficiency, negotiating power, and influence of a collaborative group.



Access the complete reference list online at

<http://www.expertconsult.com>

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